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ADVENTURES AMONG VIRUSES

III. The Puzzle of the Common Cold*

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ON A wind-swept hilltop just outside Salisbury, in southern England, stands Harvard hospital, the site of the Common Cold Research Unit. I should like to tell you today how we are attempting there to learn something about the common cold, and also why we are doing it there, why we call the place Harvard hospital and what we have learned so far. I shall also have much to say about what we don't know, and I shall discuss means by which the problem can, perhaps, be attacked.

Most of you know why our unit is called Harvard hospital, for I expect that a number of you worked there during the war or were at any rate concerned in planning it. You will know that Harvard University with the American Red Cross planned and built and shipped to England, early in the war, a prefabricated hospital, to help in the study and control of the epidemic disease that was expected to follow intensive air attack. Its first director was Dr. John E. Gordon. Later when the United States entered the war it became a military hospital and laboratory. At the end of the war it was generously handed over to our Ministry of Health with the hope that it would be used for some purpose in the field of preventive medicine.

Early in 1946 some of my colleagues and I felt that the time was ripe for a fresh attack on the problem of the common cold, for much had been learned about viruses since the investigations of Dochez and his colleagues[1] some fifteen years earlier. We adopted as our working hypothesis the view of Dochez and others that a virus was the causative agent of colds, and everything we have seen confirms that opinion. Discussion round a table brought to light the fact that Harvard hospital was standing idle, or used merely to house stores, practically asking us to come and make use of it. True, it was a little inconveniently far from London, about 90 miles, but otherwise it had every advantage. It was equipped with the plumbing, furniture, bedding, x-ray plant and other hospital equipment left behind when you gave it to us. Labor for alterations was scarce, but very little was needed to convert it to the purposes for which we wanted it — that is, to house volunteer "human guinea pigs." The Medical Research Council therefore gladly took the chance of sponsoring the scientific investigations with which my colleagues and I have been concerned for the last three years.[2, 3]

Why did we want a big unit of this sort in which to study the common cold? Why not get on with it in our own laboratories? The reason is, of course, that the common cold is one of a number of diseases — infectious jaundice and herpes zoster are others — that cannot be transmitted to small laboratory animals nor cultivated conveniently in the laboratory. True, chimpanzees are susceptible to colds, as Dochez[1] showed, but they are hard to get and hard to handle in the numbers we need. Human volunteers offered the only visible possibility for an experimental attack on the problem. Such volunteers had to be kept isolated, so that we could be sure that any colds resulted from our inoculations and not from spontaneous catching of a cold from outside contacts.

Experiments with human volunteers in the United States have mostly been carried out in prisons or similar institutions, or else on small numbers of persons kept rigidly isolated in hotels or small hospital wards and paid for their services. Both these methods present administrative difficulties, and we needed relays of normal persons in considerable numbers — already we have had over 1500 volunteers, though this figure does not allow for the fact that some have returned for a second, third or even a fourth visit. For we have been able to make our unit so popular that we are positively in demand by those seeking a free ten days' holiday. We pay the traveling expenses of our victims, if necessary, from the other end of the country, and this is popular with Aberdonians wanting to see the world on the cheap, but I must disappoint you by stating that we have refused to pay fares from

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overseas, though this has been asked for. We also give, of course, free board and lodging and a little pocket money. One of the advantages of the site is that we are on the edge of open country. We do not, therefore, insist on rigid confinement to the quarters but allow volunteers to go out for country walks, provided they avoid buildings, vehicles and keep 30 feet from other persons. There are also facilities for playing table tennis, badminton and even golf; volunteers are housed in pairs and it is only with one's own partner, of course, that one can play these games. Most of our volunteers have been university students coming in vacation time; during term we have obtained others by the aid of publicity given to our needs by the press and radio. With very few exceptions, all have co-operated and loyally abided by the rules laid down.

For the benefit of those who know the hospital I will explain that we found it best to turn the hospital round, as it were, so that what used to be the residents' quarters now provide the volunteers' huts, and the original wards now form laboratories and quarters for staff.

Our methods for using these expensive experimental animals are as follows. Volunteers arrive on day 1 — a Wednesday — and are placed in isolation in their quarters as described. They have a routine clinical and x-ray examination, but nothing else is done till day 4 (Saturday) except for daily visits by the masked and gowned matron, to take temperature and pulse, and by the similarly attired doctor, to determine that no cold develops during this preliminary quarantine. He also notes what is the patient's normal base line regarding nasal secretion. Volunteers record their own symptoms daily on a sheet provided. On day 4 the material to be tested is instilled with a pipette into the nose of the recumbent patient. The material may be what we call "negative control" (that is, broth or saline solution) or positive control (filtered nasal secretions from a cold) or some material under investigation. In no case does the patient nor any clinical observer know what the patient has received till the end of the trial and after the decision about "cold or no cold" has been recorded in writing. In his daily visits the physician records signs and symptoms on a chart. The patient's own account of his symptoms naturally influences the doctor's decisions, but most emphasis is placed on the amount of nasal secretion blown on to a handkerchief both before the doctor's visit and "on request." Examination with a nasal speculum naturally reveals abnormalities when a cold is present, but trivial changes are not helpful in doubtful cases. We have also issued weighed handkerchiefs daily and after drying have measured the amount of secretion produced each day; again, the figures do not tell us much more than was learned from the simple clinical examination. Scores are compiled for severity and duration of symptoms, and thus an attempt is made to evaluate colds quantitatively. Nasal secretions from "colds," filtered or unfiltered, have in the aggregate produced colds in 137 out of 231 persons (55 per cent positive). Doubtful colds are recorded as negative. Control material (broth or saline solution) has produced two doubtful colds in 63 persons: the rest were negative.

In many ways the setup is ideal. The volunteers are happy, and they are co-operative; we obtain them without great difficulty. The precautions seem to be adequate to prevent accidental infection, since our negative controls remain negative. Nevertheless, I must point out some of our difficulties. The inoculums we use are filtered or unfiltered nose washings, usually given undiluted; they must thus contain many thousands of times the virus dose one would be likely to receive in one's nose as a result of proximity to an infectious, sneezing person. The washings we use will produce a reasonable number of colds after dilution 100 times, but that is about the limit. Even with our best washings we get takes in only about 60 per cent of our volunteers. Thus, 40 per cent of our "animals" resist our inoculations, and the others get colds only because we give them an enormous dose of virus. We strongly suspect that catching a cold in real life depends on receiving quite a small dose of virus at a time when one's defenses are momentarily off their guard — looking the other way. Our studies, in our present state of knowledge, deal only with what happens when one gives a very big dose to a rather resistant person. Any one kind of test inoculum is given to at least 4 people — 2 pairs — more often to 3 pairs. You will appreciate that when, at best, 60 per cent of people "take," the laws of chance make it difficult to interpret results obtained on such small numbers of varyingly susceptible people. Negative results in particular have to be accepted with caution. Again and again a test on a small group has given an exciting and suggestive result, and we have used up many valuable volunteers following a lead that has proved only a will-o'-the-wisp.

Another trouble has been due to the fact that our volunteers reach us from an environment that is presumably contaminated with cold virus. In almost every trial a few volunteers develop colds or are found not completely free from suspicion of colds during the preliminary three days' quarantine. This means that they *and their partners* have to be excluded from the main experiment, though we usually manage to make use of them for some subsidiary work of an observational nature. Again, our broth and saline controls do not provoke colds, but other substances, such as suspensions of normal egg-yolk sac, produce mild colds in small numbers.

At one time we thought we had successfully cultivated cold virus in eggs, but tests with more uninoculated eggs revealed that we had added one more to our unique collection of will-o'-the-wisps.

No wonder that our main objective has been and will be to find a way of studying the common cold without, or with very little, use of human volunteers. If only we could cultivate and, if possible, see the virus, or produce infection in some convenient small animal, or persuade it, say, to agglutinate red cells, we could open the floodgates to such a spate of profitable work as would keep dozens of laboratories happily and profitably occupied for dozens of years. So far, however, we have not succeeded in this objective. We have not satisfied ourselves that we can cultivate the virus by any one of many available technics in fertile hens' eggs. We are aware that others have claimed to have succeeded in this endeavor; we can only say that we have not been so fortunate. We have attempted — in vain — to produce colds in mice, rats, guinea pigs, cotton rats, rabbits, voles, hamsters, gray squirrels, hedgehogs, ferrets, kittens, pigs, green monkeys, red patas monkeys, capuchin monkeys, baboons and a sooty mangabey. From several species we have attempted to recover virus and reinfect human beings — but again without success. There is plenty of scope yet for other workers, since the possibilities of the giraffe, the duck-billed platypus and (especially) the proboscis monkey and the elephant remain unexplored. We do not forget that with other viruses, such as rinderpest and dengue, success has been achieved in infecting an egg or small animal with only one or two strains of many tested. So a lucky break may come at any time.

Despite the failure, as yet, to attain this primary objective we have learned a lot; some information has accrued quite incidentally, and some has been obtained by deliberate experiment.

In the first category comes knowledge about the range of clinical symptoms produced by a single "pedigree" strain of cold virus, kept going by passage from one volunteer to another. The symptoms closely correspond with those of the commonest type of cold prevalent in Britain. Fever is rare. Malaise and headache at onset are common. Nasal discharge is the rule, serous at first, purulent later. Roughness or soreness of throat was present at the onset in 61 cases out of 88, and about a third had a cough, usually unproductive. Duration of colds was usually less than a week — that is, rather less than that of most "wild" colds. However, a number of volunteers have reported recrudescence or exacerbations of their colds after returning home; possibly they pick up secondary invaders in the outside world.

The incubation period has much the most frequently been two or three days. Relatively rarely has this been as short as twenty-four hours — a result contrasting with some of those reported from the United States.

Some knowledge has been gained of the physical properties of the virus. Filtration through graded collodion membranes indicates a particle size rather less than that of influenza virus. This is about 0.1 μ or 100 mμ across. The experiment shows the difficulty in interpreting results obtained on small groups of subjects. Clearly, the virus has passed the membranes with pores 120 to 140 mμ across, but are we to lay stress on the one definite cold produced from a 57 to 68 mμ filtrate? If this is genuine the probable size of the virus is around 20 mμ or less. If it is a false result, the probable size would be regarded as about 50 mμ. The question is of some importance, for it would be well worth while attempting with refined optical methods to photograph a virus 50 mμ across. One would have much less hope of success with something of half that diameter. I should say something at this point about the prospects of photographing a virus such as this. It is often asked whether the cold virus cannot be depicted by the aid of the electron microscope. Almost certainly it is within the range of sizes accessible to this instrument, but all success in this field depends on first learning how to obtain virus particles in a state of reasonable abundance and purity. That tame, amenable, domestic creature, the influenza virus, was never photographed satisfactorily until we had first learned how to grow it in quantity in embryonic fluids of fertile eggs. So we are back again against the dire need for a way of growing the virus of the common cold.

We have also learned something of the stability of the virus. It will survive for two years, perhaps longer, in the dry-ice containers at –76°C. It will last for days — we don't know quite how long — at ordinary icebox temperatures. We can recover it after drying in the air on a pocket handkerchief, though not in large amount. Virus has been recovered from subjects as early as twenty-four hours after infection — that is, in the incubation period and twenty-four hours before symptoms appeared. A single titration indicated that it was perhaps as plentiful then as when the cold was full blown. Our impression is that later in the cold, washings are less potent, but we have had takes from washings obtained on the seventh day. It is hard to produce deliberate cross-infection from a cold sufferer to a normal person. In one experiment involving 4 infected "donors" and 19 normal "recipients" exposed to them, only one cold was apparently transferred, and that in a person exposed to others who were in the symptom-free incubation period. Such a finding accords with my earlier suggestion that our volunteers are resistant animals. What the basis of that resistance is we do not know. In four experiments we have sought to determine whether or not antibodies are present in serums of "convalescents." The results indicate that human serum

may have inactivating properties. We cannot, of course, be sure that true specific antibodies are present. If they are, I suspect they will be found in all normal adults, "convalescent" or otherwise, just as antibodies to herpes virus are found in all who are liable to attacks of herpes.

Our attempts to cultivate the cold virus have been unsuccessful. We have, however, had one or two faintly encouraging results in the course of attempts, carried out by my colleague, Dr. T. Flewett, to grow the virus in tissue cultures of human embryos obtained from hysterotomies. Primary cultures in nasal epithelium from such embryos have given takes in 4 of 8 volunteers. Similar cultures in embryonic lung and in amnion have produced colds in 2 of 20 and 2 of 14 subjects respectively. Subculture has not certainly been achieved; in fact, all we can say is that virus has survived for several days at 37°C. in some of the cultures. That is, however, something, for in all other tissue-culture mediums or animal tissues the virus has quickly perished at body temperature. We could make better progress with this line of study if only we could obtain embryos more often.

If this scent peters out and other ideas we have fail to help us to find a laboratory approach to our problem, what can we do? Must we throw up our hands in despair and devote ourselves to some easier problem? We do not think so. There are many questions that *can* be answered with the aid of our present technic but very slowly, rather uncertainly (unless we do the tests again and again) and at great expense. One such line of attack is to look into the popular conception that draughts and chilling bring on colds. Many people are convinced that this happens in their own cases; others regard it as an old wives' tale. What does seem fairly certain, from the experience of Arctic explorers, such as I shall refer to later, is that chilling alone is ineffective. Chilling seems to do nothing to people who are right away from civilization; there must be a chance of contact with infection as well. We took three groups of 6 volunteers. Three pairs received a dose of virus so diluted that we expected it to produce only a few colds. Three pairs were chilled; they soaked in hot baths and then stood about undried in bathing dresses in a passage for half an hour or as long as they could bear it. In addition they wore wet socks for some hours. Most showed a drop of several degrees in body temperature, and felt rather chilly and unhappy for a time. Finally, three other pairs received the dilute virus *and* the chilling treatment. The results were encouraging. Chilling alone produced no colds. Dilute virus produced mild colds in 2 subjects, and the combined treatment, colds in 4, of which 2 were rather good ones. We were foolish enough to repeat this experiment, with a contrary result. Again chilling alone did nothing, but those with virus alone had on this occasion twice as many colds as those having the chilling treatment in addition to virus. So we have got to find a better technic for lowering resistance or else join the school of thought that dismisses the effects of draughts and wet socks as mere superstitions.

There is, we feel, much to be learned by observation and record about the epidemiology of colds. An urban community, and even a rural one, probably comprises so many criss-cross chains of infection that their disentangling is very difficult. Most of the interesting clues we have come from observations concerning isolated communities. Such isolated groups are mostly in Arctic regions, but there are enough observations from similar communities in temperate climates that we need not suspect that Arctic conditions alone explain the recorded results. With the exception of the classic studies of Paul and Freese[4] in Spitzbergen and a few others, most of the information is provided by explorers who have reported their impressions about cold epidemics in remote groups but kept no accurate records. Regarding many incidents one is in doubt whether the common cold or influenza is the infection concerned.

Let us take a look at some of the reports and see how far they take us. The fullest story is that of Paul and Freese[4] from Spitzbergen, relating that, during the winter months, colds in Spitzbergen fall to a very low figure indeed, and with the visit of the first ship in May an epidemic breaks out, involving first the storekeeper who has most contact with the ship but rapidly spreading, so that within two or three weeks it attacks most of the inhabitants. Moreover, those coming in the ship may themselves fall victims. Other ships visit the island during the summer and more waves of colds may occur, but soon after the last ship has left at the end of October, the colds fall to their low winter level. Similar stories are told of other isolated communities: how little children run and hide when the ship heaves in sight, knowing of the colds it will bring. The ship-cold story is so well attested that we cannot, I think, doubt its truth; we hear it of Greenland, St. Kilda, Tristan de Cunha in the southern Atlantic and other places. In the same way we hear how in relatively small ships at sea for a long time, colds disappear a week or so out of port and do not return until another port is touched at. And, again, Arctic explorers returning to civilization promptly contract the colds from which they were free in their solitary travels. According to the Norwegian explorer, Hoel, this happens at the conclusion of an Arctic journey of only three to four months; but after longer periods in isolation, the subsequent colds are more severe.[5] It is probably a common experience with many of us that we catch colds on returning to work in September after an open-air holiday and at a time

when we are feeling particularly fit — the same sort of story as that of explorers.

The contact that provokes colds in people at the end of their isolation need not apparently be with an actual symptomatic infection, though evidence about this is not always definite. An interesting account is from Tristan de Cunha, where, it is stated, colds are brought to the island in ships making the short twelve-day journey from Capetown. Ships coming from Panama round Cape Horn do not bring colds.

Another aspect of the problem is this. Parties of Eskimos in Greenland may be separated in the winter but come together in the spring *before* the annual ship arrives: colds are common then but not so widespread or severe as when the ship calls. Again, in Spitzbergen some colds may appear when settlers from one mining settlement visit another station *before* the ship calls. It is mixing up of communities that seems to start outbreaks, and these are more severe the longer the isolation and the bigger and stranger the community with which contact ultimately occurs.

All this may be interpreted in one of two ways. On the one hand, one can carry cold virus after an infection but only for a limited time; in a small enough community the virus will soon die out. Resistance will then fall in the absence of frequent stimulation with virus to boost it up again. I may note here that many volunteers inoculated with filtrates of known activity develop transient symptoms, which would be passed over almost unnoticed if attention was not being focused on the nose. We incline to believe that most colds "abort" spontaneously, and only a few break right through our defenses. If this is so, our immunity is probably being kept up all the time by subclinical or almost subclinical infections.

A second explanation is that there are many cold viruses, that isolated communities tend to develop a similar flora of such agents, perhaps preserving one to which they became resistant and losing others. They will then be susceptible after a period of months to these lost agents when they ultimately meet them again. Apparently conflicting with such a view are the experiments of Dingle and his colleagues on immunity to colds.[6] They found no evidence of resistance on the part of persons infected nineteen days earlier with virus *of the same strain*. We, also, find that the susceptibility of our volunteers is not evidently dependent on the time that has elapsed since their last cold. I stated earlier my belief that our experimental colds (and Dingle's also) might be the result of overwhelming the resistance of our subjects with a colossal dose of virus. Immunity studies in such circumstances could well fail to show up subtle differences in strains such as might be important in real life. In my more speculative moments I have toyed with a hypothesis that is a variant of that of multiple strains. Perhaps at the end of a cold, the virus persists in an avirulent phase (like a rough pneumococcus) but by losing one or other of a *series* of several constituents A, B, C and so forth. Some people we meet may be carrying cold virus minus factor A, others virus minus factor B, and so on. In a large community there is frequent opportunity for exchange of flora and recombinations that might reconstitute the complete, effective, virus; one's thoughts are naturally guided by recent work by Hershey and Rotman[7] and Luria and Dulbecco[8] on genetic recombinations among bacterial viruses. We have tested this wild idea in one experiment in which we took washings from 26 normal people, waited to make sure none of them were incubating colds and then pooled the washings, filtered them and inoculated 22 people with the pool. We did produce some colds in this way, — one, at least, was a beauty, — but one would have to do much work on those lines before being able to interpret any results.

I wish to make again this point, which I consider important. Most of the very interesting and suggestive information from the corners of the earth has come to us incidentally, from relatively untrained observers, faced by remarkable facts that they could hardly fail to notice. Some of the evidence is conflicting, and many stories are incomplete. What is needed is systematically collected and recorded information, made by people who are out to get the facts. Do ships *always* bring colds to remote communities? If not, when do they and when don't they? Must there be a cold sufferer on the boat? Could cold virus be recovered if washings were collected from remote groups, frozen or dried and brought home for study? One believes that if the need for accurate information were better known, there must be doctors in remote parts who would keep records and send them to interested workers. An alternative is to send observers to distant parts, but there are difficulties in this plan: an observer in every isolated spot is not easy to arrange for, and if one observer visits many isolated spots, the spots *ipso facto* cease to be isolated. Our researches at Salisbury cost quite a lot of money, but I could suggest plans of work costing far more: one could plant small groups of people in isolated places, seek virus in their noses at intervals, test their susceptibility to a virus inoculation at intervals, separate a group in two and re-unite it later. One can think of many things to do under controlled conditions that might tell us whether there were multiple strains of virus and answer many other epidemiologic conundrums.

Coming nearer home, there are other possibilities of learning something rather more easily by epidemiologic studies in rural communities. Near Salisbury is a beautiful valley containing a string of small villages, inhabited by people most of whom have little contact beyond their valley. My col-

league, Dr. Sommerville, visits all the schools in the valley every week and makes more detailed enquiries in one of the villages; he is gradually building up a body of facts concerning the occurrence and spread of colds in such a community.

Do colds in a household usually start among the children and spread to adults? Does the cold virus produce a different clinical picture in very small children? Do colds reach a rural family as a result of contact with the town? How do season and weather affect the incidence? There are many questions one might hope to answer from such studies. We know, of course, that we are not pioneers in this field; Dr. Frost in this country and Dr. Pickles at home in Yorkshire have shown the way.

Careful recording of personal experiences regarding colds might also help. A cold, someone may tell us, always attacks him when he gets his feet wet. There is probably no recorded evidence in the world on such a simple matter as how often such a man gets his feet wet without catching a cold or gets the cold without wetting his feet.

How does cold infection get about? Do we get infected in crowded public transport, or is it usually elsewhere? The Medical Research Council's Air Hygiene Unit shares the Salisbury site with the Common Cold Unit, and works closely together with it. Their joint studies are directed largely to studying spread of infection. The idea of the importance of the very small droplet nucleus has been popularized by Wells[9] — the notion that infective particles 10 μ or less in diameter may float for an hour or so in the air. Such germ-bearing particles may very well infect a susceptible infant with measles, but studies at Salisbury make us doubt whether such small doses of infection can avail to infect a town-dwelling adult with a cold — an adult with perhaps considerable resistance to overcome.

Apart from the obvious risk one runs in getting into the direct line of a sneeze, there are other possible channels of infection. There is the dried virus, which may be shaken off a handkerchief, which you perhaps flap once before you blow your nose. Studies at Salisbury by Dumbell, Lovelock and Lowbury[10] have disclosed methods of impregnating handkerchiefs with disinfectants — methods that kill most of the staphylococci *in situ* and probably the cold virus also. Do we know that these handkerchiefs are dangerous and do really shed cold virus as well as staphylococci into the air? Tests for virus in extracts of fresh wet handkerchiefs and of handkerchiefs dried in the air have shown the presence of virus, but, on the whole, less than we should expect to find if they were a very great menace. We need to know much more about the persistence of cold virus on fabrics. Another of the travelers' tales from the Arctic — and this comes from more than one source — records an outbreak of colds when clothes were unpacked from crates many months after the party had left their base at home. Certain knowledge about whether these were real virus colds would be very helpful to our understanding of the epidemiology of colds at home.

Finally, the Salisbury studies touch on the danger of manual contact in spreading colds. The use of a little fluorescein, so little as to be invisible with ordinary light but very bright under ultraviolet rays, has been revealing. An artificial running cold has been produced by fixing a reservoir with a fine capillary outflow on a subject's nose; the reservoir contains a viscous fluid with a little fluorescein. The subject behaves normally and blows his nose when he feels the need. The fluorescein is found to get everywhere — mostly on to his handkerchief, much on his hands, his face, all over the room in fact, even on to the food he or his companion is about to eat. However, in one experiment oral infection with cold virus was unsuccessful. Saliva, or rather the secretions from the front of a subject's mouth, on the other hand, contained plenty of virus.

I have, I hope, made clear how much about colds we don't know, and how slow our increase of knowledge is bound to be, unless someone can find a trustworthy method of laboratory study: may that day come soon! But whether it does or does not, there are many ways of approaching the problem, which is at present obscured by the mists of folklore, superstition and pseudoscience. Almost everyone has his own foolproof technic for preventing or curing colds; yet colds are as numerous and as troublesome as ever. I will go so far as to warn the nonmedical members of this audience that even the most eminent men of science almost invariably lose all sense of critical judgment when colds and especially their own colds are concerned, and the statistical methods they use in their daily work are all forgotten. I am, however, confident that, even if it is the last human infection to be overcome, science will banish the common cold in the end.

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ACUTE SUPPURATIVE TENOSYNOVITIS OF THE HAND*

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SUPPURATIVE inflammation of the flexor tendons of the hand presents a controversial problem, and one that has not been solved surgically.

The incidence and complications of acute suppurative tenosynovitis have decreased since the advent of antibiotics. However, this serious infection is still encountered too frequently.

Analysis of Study

The material studied consisted of 100 cases of acute pyogenic infection of the flexor tendon sheaths of the hand, previous to antibiotics, and 50 cases since the advent of antibiotics, in which patients were treated at the Boston City Hospital.

The origin of the infection has not changed since the advent of antibiotics. It has been either a case of direct inoculation of the tendon sheath or an indirect one in which the infection spread from a neighboring pathologic process. In these series 59 per cent were of direct, and 41 per cent of indirect origin. In no case in these series did the infection spread via the blood stream. Eight cases of gonococcal tenosynovitis, which were blood borne, are not included in these series. In no case did the infection spread via the lymphatic system. Forssell[1] reported cases of lymphatic origin, and Kanavel[2] also believed that such infection could be of lymphatic origin.

The cases were classified on the basis of functional result,[3] as follows:

Group I. Those with optimum results included cases with normal or almost normal function of tendons and those with complete or almost complete motion of all finger joints. There may be slight limitation of extreme flexion. Function of fingers is practically as good as before infection.

Group II. Cases with fair results include partial function of tendons, the limitation usually being caused by adhesions, and active, but limited, motion in the proximal or distal interphalangeal joints or both. There may be normal or slightly limited motion in the metacarpophalangeal joint, fist cannot be made actively, but adjoining fingers may be used for extreme flexion.

Group III. Cases with poor results include sloughed tendons with loss of flexion of the middle or distal phalanx, or both, and ankylosed proximal or distal interphalangeal joint, causing a stiff finger (motions in the metacarpophalangeal joint may or may not be present) as well as amputations and deaths.

Puncture wounds have been found to be the most common type of injury causing septic tenosynovitis. In infections of direct origin, puncture wounds occurred in 37 per cent, lacerations in 18 per cent, and compound dislocation and gunshot wounds in 2 per cent each. In infections of indirect origin, puncture wounds occurred in 5 per cent, lacerations in 12 per cent, abrasions in 8 per cent, human bite and felon in 6 per cent each, contusions and burns in 2 per cent, and bleb and septic callus in 1 per cent each.

The primary site of infection in 50 per cent of the cases was the transverse volar creases, where anatomically the tendon sheath is devoid of its fibrous layer. The distal volar crease was the site in 27 per cent of the entire series, the middle volar crease in 16 per cent, and the proximal volar crease in 7 per cent. The closed spaces of the fingers were the primary site in 37 per cent of cases, the distal closed space in 17 per cent of the entire series, the middle closed space in 12 per cent, and the proximal closed space in 8 per cent. The dorsum of the hand was the site of the infection in 12 per cent, and the entire finger in 1 per cent.

Table 1. *Time Factor in Acute Suppurative Tenosynovitis.*

Result	Previous to Antibiotics			Since Antibiotics		
	Average duration of infection	Minimum duration of infection	Maximum duration of infection	Average duration of infection	Minimum duration of infection	Maximum duration of infection
	days	*days*	*days*	*days*	*days*	*days*
Optimum (Group I)	2.3	Less than 1*	5	2.0	1	6
Fair (Group II)	5.0	2	9	5.6	2	8
Poor (Group III)	6.0	2	11	5.8	3	11

*20 hours.

A most important factor influencing the end result is the time elapsed between the onset of infection and operation, or the delay in operation. However, time is not the only significant factor; some hands operated upon within twenty-four hours did poorly, whereas others operated upon after five days did well. Antibiotics seem to aid in obtaining good results in delayed cases, but with these drugs there is a tendency for some to delay too long before advising operation for these severe infections.

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Table 1 shows the relation of the duration of the infection and the results in each series.

The bacteriology has not changed appreciably except for the fact that there have been fewer mixed infections since the advent of antibiotics. Almost invariably mixed infections have caused poor results. Antibiotics, by controlling mixed infections, have decreased the incidence of severe complications.

Table 2 is a summary of the bacteriology in 100 cases previous to antibiotics. Table 3 is a summary of the bacteriology in 50 cases since the advent of antibiotics.

These series indicate that acute suppurative tenosynovitis is about 42 per cent as common since the use of antibiotics as it was before these drugs were widely available. One hundred cases were encountered over about a five-year period from 1938 to 1942. Fifty cases have been seen over a six-year period from 1943 to 1948. However, with new antibiotics gradually becoming available since 1942, the incidence will probably be less over the next six-year period. This probability is presented in the fact that 12 cases were encountered in 1943 and 6 cases in 1948.

With antibiotics as an adjunct to surgery, the number of optimum results has been more than doubled, and the number of poor results is about a third of what it was before the use of antibiotics. Table 4 shows the comparative end results in both series.

The incidence and severity of all complications have decreased since the use of antibiotics (Table 5). In our first series tendon slough occurred in 41 per cent and was the commonest cause of poor results.[3] The incidence of this complication has decreased to 6 per cent in our later series.

TABLE 2. *Bacteriology before Antibiotics.*

Organism	Results		
	Group I	Group II	Group III
Streptococcus haemolyticus	12	10	17
Str. haemolyticus and Staphylococcus aureus	4	6	19
Staph. aureus	16	4	1
Str. haemolyticus, Staph. aureus and *Borrelia vincentii*	0	0	6
Staph. albus	0	0	1
Staph. aureus, Proteus vulgaris and diphtheroids	0	0	2
Str. haemolyticus, Escherichia coli and *Bacillus subtilis*	0	0	1
Str. haemolyticus, Staph. aureus and diphtheroids	0	0	1

TABLE 3. *Bacteriology Since Advent of Antibiotics.*

Organism	Results		
	Group I	Group II	Group III
Str. haemolyticus	14	3	2
Str. viridans	3	1	0
Staph. aureus	10	2	1
Staph. albus	3	0	0
Str. haemolyticus and *Staph. albus*	4	2	3
Str. haemolyticus, Staph. aureus and diphtheroids	0	0	1
Str. haemolyticus, Proteus vulgaris and *Borrelia vincentii*	0	0	1

TABLE 4. *Comparative End Results.*

Treatment	Period	No. of Cases	Good Results	Fair Results	Poor Results
Operation without antibiotics	1938–1942	100	33	20	47
Operation in addition to antibiotics	1943–1948	50	68	16	16

TABLE 5. *Comparative Complications.*

Complication	Operation without Antibiotics	Operation in Addition to Antibiotics
	%	%
Mortality	2	0
Amputations	18	8
Tendon slough	41	6
Osteomyelitis	31	12
Thenar-space abscess	18	2
Mid-palmar-space abscess	12	2
Septic arthritis	9	2
Radial bursitis:		
In palm	10	2
At wrist	8	0
Ulnar bursitis:		
In palm	6	0
At wrist	3	0
Abscess of intermuscular space of forearm	3	0

Treatment

Since penicillin has become universally available, most reports on the therapy of acute suppurative tenosynovitis have stressed the good results obtained with the removal of pus through a small opening in the sheath and the local application of penicillin. This type of therapy was apparently stimulated by reports of good results with local penicillin treatment in infections of other cavities, particularly the pleural cavity and some joint cavities.

Five methods with local penicillin therapy are considered. Florey and Williams[4] suggest that a lateral incision be made over the affected digit. The tendon sheath is opened along the length of the digit and in the palm. The wound is then covered with calcium salt of penicillin and packed with gauze soaked with penicillin paste. Postoperatively, the penicillin-paste dressings are changed every twenty-four hours until cultures are negative. Active motion is begun after the fifth day. The results in 11 cases were optimum in 5, fair in 4 and poor in 2.

Burt[5] advises a lateral incision made over the proximal phalanx and carried through the tendon sheath, the pus being evacuated. A fine-rubber catheter is then inserted into the tendon sheath. A

cotton stitch closes the skin, and this suture is tied about the rubber tube. The procedure is repeated over the middle phalanx on the same or on the opposite side. A dressing is applied with the rubber tubes extending out of the dressing. A dorsal splint is moulded to the dorsum of the hand, wrist and forearm. Every three hours 0.5 cc. of penicillin solution is injected through the tubes; each cubic centimeter of solution contains 250 units of penicillin. This treatment is continued for five days. The rubber tubes are removed and active motions are begun. Burt's results in 3 cases were optimum, fair and poor in 1 each.

Marsden[6] recommends the use of two small, transverse incisions, each about 0.6 cm. long, one of which is just proximal to the metacarpophalangeal crease, the other is just proximal to the distal interphalangeal crease. The incisions are carried down to the tendon sheath, and tiny nicks are made in the sheath. Needles, of about 18 bore, are inserted into each incision, through the tendon sheath until the periosteum is reached. This ensures that the needle is actually in the tendon sheath. Pus is aspirated from the tendon sheath through either needle with a dry, sterile syringe. A 1-cc. solution of penicillin, containing 500 units of the drug, is injected through one needle until it appears through the other needle; the penicillin is thus washed through the infected sheath. The needles are withdrawn, and both incisions are packed with dry, sterile packing gauze to keep them open.

The needles are reinserted daily, and penicillin is injected locally, after morphine has been injected; 15,000 units of penicillin is injected intramuscularly every three hours. Active motions are started immediately with penicillin therapy. Local treatment is gradually "tailed off" as the local condition improves and as the swabs become free from pathogenic bacteria. Marsden reported optimum results in 5 cases, fair results in 3 and poor results in 2.

Unonius[7] makes a small, curved incision, with the convexity distal, across the volar aspect of the finger and close to a joint, or over the point of maximum tenderness, or over a subcuticular abscess. The tendon sheath is opened by a crosscut incision. Thin ureteral catheters are introduced into the sheath proximally and distally. When the incision is made at the end of the tendon sheath, only one catheter is used. Catheters are fixed to the skin with silk, and the tendon sheath is flooded with physiologic saline solution until clear fluid returns. Then 0.2 to 0.6 cc. of penicillin, containing 5000 units per cubic centimeter, is injected. Flooding and injecting with penicillin solution continues every four to six hours until the fluid contains no bacteria on direct examination. For a few days, the finger is immobilized in a bandage, after which hand baths and active motions are begun. Unonius reports the following results in 8 cases: optimum in 5, fair in 2 and poor in 1.

Loudon, Miniero and Scott[8] have classified acute suppurative tenosynovitis into three degrees. The severe third-degree infection contains slough that must be excised. For the less severe first-degree and second-degree infections, a short transverse incision, a so-called observation incision, over the distal end is suggested. If the tendon sheath is found to be distended with exudate and to have lost its normal transparency, the sheath is opened and washed out with saline solution from the proximal end by introduction of a needle. When the needle is in the sheath no resistance is felt to the injection. However, if difficulty is encountered, the proximal end of the sheath can be exposed through a short, transverse incision parallel and distal to the distal palmar crease. With the same needle, 10,000 units of sodium penicillin in 5 cc. of distilled water is injected into the sheath, and the observation incision is closed; 20,000 units of sodium penicillin is injected intramuscularly twice a day for five days postoperatively. The hand is immobilized until healing occurs. The results in 7 cases were optimum in 5, fair in none and poor in 2.

The cases presented by those recommending local penicillin therapy for acute suppurative tenosynovitis are too few in each group to permit definite conclusions about ultimate results. The injection of penicillin locally into the tendon sheath, by most of the methods reviewed, is a blind method of therapy. Infective material could be forced into the radial and ulnar bursas and the midpalmar and thenar spaces by the blind injection of penicillin into the infected tendon sheaths. The daily insertion of needles into infected sheaths must be a painful procedure.

The parenteral administration of penicillin is considered more logical than the local use. With adequate circulation in the involved part, the concentration of penicillin in the blood stream may be kept at the proper level to control the infection. With adequate circulation and the use of local penicillin only, all recesses of the infection may not be reached. With inadequate circulation in the infected part, neither parenteral nor local penicillin will prevent a poor result.

Intra-arterial injection of penicillin has been recommended by some for the treatment of acute suppurative tenosynovitis. The reason seems to be that there is an excess of edema in the infected region and intra-arterial administration may give a local increased concentration of penicillin in the infected site. The possible dangers with this route outweigh the possible good, especially the danger of arterial spasm in a region with a damaged circulation.

Active motion should not be instituted until the infection has subsided.

The results with incision and drainage of all recesses of the infection, together with parenteral administration of penicillin, are better than those with most methods of local penicillin therapy.

Discussion

A wide incision and drainage of the involved tendon sheath, one local irrigation and large intramuscular doses of penicillin are preferred.

A longitudinal incision is made over the medial or lateral aspect of a finger from the base of the distal phalanx to the base of the proximal phalanx. A 1.3-cm. longitudinal, palmar incision is made to drain the palmar aspect of the sheath. All slough is removed. A small bridge of the proximal annular ligament is left intact to prevent bowing of the tendon. The opened tendon sheath is irrigated from the proximal end with saline solution; 50,000 units of penicillin in 5 cc. of saline solution is injected into the proximal end of the tendon sheath. A rubber-tissue drain is kept in place for twenty-four to forty-eight hours.

Figure 1 shows incisions for tendon-sheath and bursa infections. Postoperatively, the hand is immobilized in an aluminum splint in a position of function until the infection subsides. Hot fomentations are used, and 100,000 units of penicillin is given intravenously immediately postoperatively; 100,000 units of penicillin is given intramuscularly every three hours until the infection subsides, when active motions are begun.

Figure 1. *Incisions for Draining Infected Tendon Sheaths, Radial and Ulnar Bursas, Spaces in the Wrist and Forearm (Reproduced from Flynn[3] with the Permission of the Publisher). The dotted line represents a rarely used incision.*

Table 6. *Comparison of Results.*

Author	No. of Cases	Good Results	Fair Results	Poor Results
Local penicillin treatment:				
Florey and Williams[4]	11	5 (45.4%)	4 (36.4%)	2 (18.2%)
Burt[5]	3	1 (33.3%)	1 (33.3%)	1 (33.3%)
Marsden[6]	10	5 (50%)	3 (30%)	2 (20%)
Unonius[7]	8	5 (62.5%)	2 (25%)	1 (12.5%)
Loudon, Miniero and Scott[8]	7	5 (71%)	0	2 (29%)
Adequate operation in addition to parenteral administration of penicillin:				
Boston City Hospital series	50	34 (68%)	8 (16%)	8 (16%)

Table 6 compares the results of "local penicillin" therapy with those after wide incision and drainage and parenteral administration of penicillin.

Summary

Three changes in acute suppurative tenosynovitis of the hand have been noted since the advent of antibiotics. The incidence has decreased to 42 per cent of that previous to the introduction of antibiotics. The incidence will probably be less in the next six years. The complications are less in severity and fewer in number. The results are about twice as good as those before antibiotics were used.

Local penicillin therapy is not considered the ideal treatment for acute suppurative tenosynovitis. An adequate incision for drainage of all recesses of the infection, the removal of all pus and slough and the parenteral administration of penicillin are preferred.

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DIABETES*

Certain Basic Considerations

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BECAUSE of present interest in the detection of the patient with unrecognized diabetes and more especially as a result of thirty years as chief of the Diabetic Clinic at Boston City Hospital, I should like to present a few basic considerations in relation to this disease.

Diagnosis

A single positive urine test does not mean diabetes, nor does a single negative test exclude it. An accurate diagnosis cannot be made without both urine and blood studies, and even then there are many cases in which the diagnosis may remain in doubt. Given the typical diabetic symptoms of weight loss, polydipsia and polyphagia, together with glycosuria, nine times out of ten the diagnosis of diabetes is correct without a blood sugar determination. However, many diabetic patients have no symptoms and exhibit glycosuria only occasionally. Briefly, there are a few rules that will aid in a positive diagnosis.

Glycosuria in addition to a fasting blood sugar of 130 mg. per 100 cc. or over means diabetes. Glycosuria and a normal fasting blood sugar may or may not mean diabetes. In such cases some sort of tolerance test must be done. Examination of the urine and blood for sugar forty-five to sixty minutes after a meal liberal in carbohydrates is helpful. Glycosuria in combination with a blood sugar of 180 mg. per 100 cc. or over probably means diabetes. At any rate, the subject can be called a strong diabetic suspect.

Glucose Tolerance Test

Generally speaking, the most common procedure is to give 100 gm. of glucose after a fast of at least twelve hours and after a period of three days during which there has been no restriction of ordinary diet. Urine and blood tests are made before the glucose is ingested and at various intervals thereafter, usually periods of one, two and three hours. In the normal person one expects that the blood sugar will not rise above 180 mg. per 100 cc. and that the level will return to normal two or three hours after the glucose meal is given. Most observers agree that a peak value, even though accompanied by glycosuria, is not diagnostic of diabetes if the blood sugar returns to normal in two hours.

Differential Diagnoses and Diagnostic Pitfalls

Renal Glycosuria

In this condition glycosuria occurs without hyperglycemia. Sugar may appear in the urine at all times or may depend upon the type of diet, but at no time is there elevation of the blood sugar. This condition is not harmful and apparently never develops into true diabetes.

Sugars Other than Dextrose

Occasionally, but not frequently enough to be of practical importance, reducing substances other than dextrose are present in the urine.

In pregnancy, lactose may be present. In addition, the renal threshold in pregnancy is low. It is possible, therefore, that the sugar found is more likely to be dextrose than lactose. A blood sugar determination will satisfy diagnostic requirements and will eliminate a false sense of security, which on occasions has led to real trouble.

In addition to points already made, the underlying difficulty in all diagnostic tests for mild diabetes is due first to the fact that the rate of absorption of glucose and also the renal threshold for sugar may change from time to time, and secondly to the fact that there are a number of diseases that may influence the blood sugar level, such as infections, recent injuries, acute alcoholism, hyperthyroidism, hypertension, certain adrenal tumors, encephalopathies, coronary occlusion, renal failure and arteriosclerotic changes in the kidney.

Accordingly, it is difficult to see how one has any right to make a positive diagnosis of diabetes without certain laboratory tests as heretofore enumerated, as well as a carefully taken history and physical examination of the patient.

Detection Drives

Sponsored by the American Diabetes Association and the United States Public Health Service and other interested professional and lay groups, a campaign to discover the cases of unknown diabetes is underway.

All observers agree that the discovery of hitherto unsuspected diabetes is of tremendous importance. The nature of diabetes is such that if untreated the mild case frequently changes to the severe type. As a matter of fact, the physician has his best opportunity to do a real, constructive job in the intelligent management and careful follow-up study of the patient with mild diabetes. In no case should the

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finding of even a trace of sugar in the urine be disregarded. In the histories of 2000 diabetic patients at the Boston City Hospital there are several records revealing the presence of an occasional trace of sugar in the urine at a previous hospital admission, but this finding was disregarded. On subsequent readmission to the hospital, the disregarded diabetes had become sufficiently severe and fixed to require insulin. It is now readily admitted that crippling vascular disease is not limited to the severe type of diabetes but may be present in the mild type.

This whole problem is very adequately summarized by Beaser.[1] Among his conclusions is the following:

> It is known that sugar may be present in the urine for several years before symptoms pertaining to the disease become evident. This fact explains its apparent onset with complications in 19 per cent of the cases studied — the patients had had diabetes for some time but did not know it.

Regardless of all that can be said about the importance of finding the hitherto unknown case, certain other aspects of diabetes detection are worthy of careful consideration.

The first is the very important problem of erroneous diagnosis. Wilder[2] calls attention to this point but concludes that "the advantage to persons with potential diabetes of being put on their guard and thereby protected against the development of frank disease outweighs the occasional injury to persons for whom a diagnosis of diabetes is unjustified." Whether or not this point of view is accepted is unimportant. The main consideration is that there is a possibility of an erroneous positive diagnosis. Moreover, there are many cases in which patients must be observed for a period before a previously questionable diagnosis can be ruled in or out.

With due consideration of the above statements, a few conclusions seem justified:

Sufficient evidence has been presented to make clear the importance of detecting the patient with unrecognized diabetes.

Detection drives if instituted at all should include wholehearted support of physicians involved, a period of instruction for physicians regarding methods and interpretation of diagnostic procedures, and careful marshaling of various forces such as hospital clinics, health agencies, visiting nurses and social agencies to assure adequate laboratory facilities, a careful follow-up study of suspects, and, finally, a plan definitely agreed upon for reporting to some central agency or physicians' committee regarding the results of follow-up study. There is no point in merely referring a patient with a positive urine test to the family physician until one is certain that the physician will accept the responsibility involved and that proper laboratory facilities are at his disposal. Any hit-or-miss method in the diagnosis of any disease is just as likely in the long run to do harm as to do good.

On the other hand, no one can deny the value of any plan that will provide for the general practitioner good practical instruction about the diagnosis and treatment of diabetes, will make available to the doctor better and inexpensive laboratory facilities and will assist in setting up diabetic clinics as part of the services rendered by certain community hospitals. This is a job for physicians, medical societies, diabetic societies and health organizations and in my opinion should antedate, or at least coincide with, any widespread so-called "detection drive."

Management

What is the purpose of good management of the diabetic patient? In my opinion, the object is to keep all patients at work without interruption because of episodes of hypoglycemia or severe acidosis, and without serious late vascular complications as evidenced by retinal changes, heart and kidney damage and peripheral vascular disease.

Assuming that the accomplishment of the above objective requires good management, what is meant by this statement? Here one meets with certain differences of opinion. There are those who interpret good treatment as meaning that the urine should be sugar free and the blood sugar within normal limits at all times. There are others who believe that good control is maintained if the morning urine is either sugar free or nearly so, but they are not worried if some of the specimens during the day show from 10 to 20 gm. of sugar and are content if the fasting blood sugar averages under 200 mg. per 100 cc. Finally, there are those who are not concerned about either the amount of sugar in the urine or the level of the blood sugar so long as the patient maintains weight and strength and exhibits neither polyuria nor acetonuria.

Mosenthal[3] has classified these three groups as purists, middle-of-the-roaders and free dieters.

In my opinion the whole subject of diabetic control may be briefly summarized as follows: in the newly discovered case it is probably desirable to treat the patient vigorously — in other words, to try to keep both urine and blood sugar normal in the hope that rapid actual pancreatic regeneration may result. In 1940 McDaniel et al.[4] found that "Early vigorous treatment brought about an amelioration in the diabetic condition of far greater degree than one would anticipate."

Once it has been determined that there is no hope for rapid pancreatic regeneration, or once it is clear that the patient needs 30 units of insulin or more, vigorous so-called purist treatment may not be necessary or practicable. In other words, according to Mosenthal,[3] a conservative attitude may be advisable. The problem here is to keep the diabetes in as good control as possible without

interruption by insulin reaction or acidosis. At this point a few words about the experience at the Boston City Hospital are of interest. In this clinic, the treatment of diabetic patients is almost always of the conservative type, — with an effort to keep patients at work and with particular care to avoid insulin reactions. This means that most of the patients have some glycosuria at times during the day and that the fasting blood sugar levels are seldom within normal limits. Also, little or no attention is paid to high blood sugar levels without glycosuria, in the belief that hyperglycemia without glycosuria is not harmful. Nevertheless, in an appreciable number of these patients it has been possible over the years to reduce the amount of insulin and in not a few insulin has been discontinued. (Owing to the untimely death of the physician who was conducting this study, the exact details are not available.) It is apparent, therefore, that even under so-called "middle-of-the-road management" pancreatic improvement may take place.

Finally, this clinic has had no experience with the so-called "free dieting" type of treatment as advocated by Tolstoi et al.[5, 6]

Diet

In general, the diabetic diet does not differ greatly from the average diet. Most patients receive at least 150 gm. of carbohydrates, and many receive as high as 300 gm. The fat is definitely reduced, — 80 to 150 gm., — and the protein should be rather high — 100 to 150 gm. It seems to me that a rather high level of carbohydrate (200 gm. or more) and of protein (100 to 150 gm.), with a fat diet less than 150 gm., is about right.

Weighed Diets

In the clinic at Boston City Hospital, it has not been possible to use weighed diets, for which I can see no necessity. Printed diets, using household equivalents, are sufficiently accurate for all practicable purposes. Certainly, in the type of working person under consideration, this type of diet has worked satisfactorily. However, one good way to learn about diet values is to be forced to weigh the diet.

In summary, the objective of treatment is to maintain weight and strength, to keep the diabetic patient at work and to avoid complications. This can be accomplished by a diet sufficient for the patient's needs — a diet adjusted to add weight or to reduce weight as the situation requires, liberal in carbohydrates, fairly liberal in protein and rather low in fat. Sufficient insulin should be given to keep the diabetes in as good control as possible, the physician always remembering that insulin reactions are to be avoided.

Complications

Obviously the best way to treat diabetic complications is to prevent them and the second best way is to discover them early.

Education of the patient, advocated by the Joslin group, is of great value. Education of the general practitioner to include simplification of methods, and improvement in laboratory facilities, is equally important but, in my opinion, has been neglected.

The physician who assumes the responsibility for treating a diabetic patient needs to know a few simple rules. There is no mystery about dietetic management — weighed diets are not necessary; all the physician needs is a very simple printed program, easily understood by both himself and the patient. Insulin is a potent drug; its institution should be started slowly, and changes made gradually. The presence of acidosis is a definite danger signal, requiring vigorous treatment for at least a brief period. In every case careful attention should be directed to the state of the peripheral circulation, and to the patient's general physical condition.

Too often patients have been admitted to the Boston City Hospital in severe insulin shock, others have been in acidotic coma for so long before admission that their chances of recovery are without hope, and still others exhibit well advanced peripheral vascular complications. This brings into sharp focus the important question, How often should the diabetic patient be seen by his physician? Obviously, this depends entirely upon circumstances. Some patients need to be seen once a year, and others may need attention every day or several times a day. The main point is that the responsibility rests entirely upon the physician himself.

In conclusion, once the physician assumes the responsibility for treating a diabetic patient, he must know a few simple rules regarding management, and he must make it *his* business to see the patient as often as he deems it necessary. Only in this way can complications be prevented, or at least given early treatment.

For the purposes of this discussion, only two complications are considered: acidosis and coma and vascular degenerative disease.

Acidosis and Coma

Frequently, the precipitating factor in diabetic acidosis is not clear, but in all probability some infection is the most common cause. It is a safe rule, therefore, to anticipate this. X-ray examination of the chest, blood cultures and complete urinalysis should be the rule in any case of severe acidosis. It is well to remember that in the badly dehydrated patient frank pneumonia may be present without any demonstrable physical signs.

Secondly, so far as statistical data are concerned, and also (and I believe this to be important) so far as the proper point of view of both the public and the general practitioner is concerned, it would be a great help if those interested in diabetes could unite on what is meant by the term "diabetic coma."

In some clinics all patients with blood carbon dioxide values of 20 vol. per cent or lower are considered to be in "coma," and in other clinics the term "coma" is used to designate only the unconscious patient. The unlicensed use of the word "coma" can be confusing and at times discouraging.

At the Boston City Hospital diabetic patients in coma present a real problem, and deaths do occur. On the other hand, regardless of the degree of acidosis, the management of the conscious patient presents no serious problem despite the fact that in this group blood carbon dioxide values may be as low as 8 vol. per cent.

Vascular Disease

The problem of vascular degenerative disease *in diabetes* or *associated with diabetes* is now brought sharply to attention as a result of recent reports in the literature.

In addition to clinical reports by White,[7] Dolger[8] and others, an important pathological report has been presented by Robbins and Tucker.[9] In an analysis of 307 cases of diabetes at autopsy at the Boston City Hospital, using 2800 post-mortem examinations in patients without diabetes as a basis for comparison, the authors concluded as follows:

> The diabetic patient lives as long as the nondiabetic. There are, however, certain hazards that he is seemingly more likely to encounter, namely, coronary occlusion, peripheral vascular disease, infections of the extremities and acute pyelonephritis.

Furthermore, at the Boston City Hospital the youngest patient with myocardial infarction on record in the Heart Station is a diabetic patient who had her attack at the age of eighteen, five years after the onset of diabetes. (Incidentally this patient is living and at the age of twenty-nine gave birth to a healthy baby.) In addition there is the record of a patient whose diabetes first appeared at the age of twenty-seven; at the age of thirty-one a lower-leg amputation was necessary, and at the age of forty-three this patient died as a result of a myocardial infarction, and by this time he was totally blind.

Despite the importance of this problem, there is no point in adopting a pessimistic point of view. Very definitely there is another side to the story. There are many patients (probably more than one knows about) who have survived twenty-five years of the disease and who are to all intents and purposes perfectly well. Many more (as indicated by the study at the Boston City Hospital) have had the disease for twenty-five years or more and are not perfectly well but are able to carry on with comfort. In addition, there is always the possibility that unexplained changes will take place. For example, of a patient with relatively mild diabetes, in 1939, an excellent ophthalmologist wrote as follows: "a central retinitis of diabetic origin." In 1947, after a period of no change in routine care, and without any specific therapy, the same ophthalmologist commented on the same patient as follows: "whatever pathology produced the central retinosis in 1939 has cleared without any loss of vision."

Sometimes physicians lose sight of the fact that the mere presence of diabetes does not mean that all things that befall the patient are of diabetic origin.

Granted that these patients are prone to develop vascular lesions, the actual cause in each case is a matter of considerable controversy. White[6] states that poor control of the diabetes parallels the severity and frequency of the lesion. On the other hand, Dolger[8] concludes that neither the age at onset nor the severity of the disease, nor the method of treatment bore any definite relation. Mosenthal[3] believes that "any hypoglycemic reaction, however mild, may entail petechial or larger hemorrhages that are prone to heal and leave no clinical effect, though some damage necessarily remains and may be cumulative with recurrent attacks." Finally, the Seminar on the Degenerative Lesions of Metabolism held in New York City in October, 1947, resulted in no definite answer to the problem.

Conclusions

Regardless of whether early vascular trouble is a complication of diabetes, whether both diabetes and vascular disease represent some inherent tendency in a given patient, or whether the age of the patient at onset, the duration of the disease and the type of treatment have anything to do with the problem, the fact remains that *apparently* some diabetic patients are more prone to have vascular trouble at an earlier age than nondiabetic persons.

The diabetic person is an ideal patient for the study of possible early vascular disease and therefore commands the attention of all physicians interested in this problem.

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VITAMIN B EXCRETION STUDIES IN PATIENTS WITH RHEUMATOID ARTHRITIS*

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THE problem of vitamin deficiency in rheumatoid arthritis has been debated for the past ten years since Steinberg[1] found abnormal bowel roentgenograms in many arthritic patients and attributed the gastrointestinal symptoms to this deficiency. After increased vitamin B consumption, many of these symptoms subsided, and he ascribed this to a need for vitamin B in arthritic patients. Race[2] was of the opinion that vitamin B deficiency produced thinning, atrophy and atonia of the gastric and intestinal membrane, leading to decreased food absorption with ultimate depletion of body reserves and increased susceptibility to secondary infection — possibly through the abnormal bowel wall.

Studies of vitamin A and C requirements at the Robert Breck Brigham Hospital conducted by Hall, Bayles and Soutter[3] and Hall, Darling and Taylor[4] on patients with rheumatoid arthritis, have shown, respectively, a relative deficiency and a lowered serum level of these vitamins as compared to normal controls. The administration of these vitamins in large therapeutic doses had no apparent effect on the course of the disease.

A review of the literature failed to reveal any recent studies of vitamin B in arthritic patients, although thiamine excretion has been investigated in a variety of other diseases. The present study was undertaken to evaluate the vitamin B nutrition of patients with rheumatoid arthritis.

It is believed by many observers that the urinary excretion of components of the vitamin B complex reflects the state of body stores of these vitamins. This gives by no means the complete picture, for the excretion varies during the day, and from day to day. Secondly, not all the excretion products are being measured. The values are used merely as a standard to compare patients and normal controls. The normal values, established by Johnson et al.,[5] apply to young soldiers under active training — thus, the average excretions, being affected by diet and activity, are probably abnormally high.

Ingested vitamin B is used to replenish body stores, utilized in metabolism with its end products excreted or excreted unchanged in the stool, urine, or sweat. There appears to be a renal threshold for these vitamins, and as the intake falls so does the urinary excretion — hence, with a minimal intake, the tissue stores will be maintained and the urinary excretion will be zero, or at very low levels.

Because of this protective mechanism of the kidney, the measurement of urinary excretion will give valuable information when it is normal, but a subnormal excretion does not necessarily mean tissue depletion. To obtain further information in these questionable cases it is necessary to give a load test — in other words, to supply the organism with excessive vitamin and measure the increased excretion as compared to the control state. If the tissue stores are adequate, the excretion will increase by the expected increment; should the tissue stores be below normal, a greater percentage will be retained and produce a lowered excretion. On deficient diets normal persons show a fall in urinary thiamine excretion within twenty-four to forty-eight hours and, after having achieved a deficient state, will continue to show low excretions in spite of a normal diet as long as tissue deficiency exists. Therefore, for adequate determination of the nutritional state in vitamin B studies, both control and load tests should be performed.

Studies by Westenbrink and Goudsmit[6] in 1937 and Melnick, Field and Robinson,[7, 8] revealed a diurnal variation in the excretion of thiamine — the morning samples being the lowest, and the evening specimens the greatest — corresponding to increased thiamine intake during the day. During the same studies it was also found that test doses given orally were more sensitive in determining deficiency than when given parenterally, since there was not the sudden "flooding" of the body by the vitamin, which may result in falsely high excretion masking a borderline deficiency. Giving the test dose in the morning fasting state modifies the excretion by allowing for more rapid absorption. These varying factors make it difficult to compare results as reported in the literature, for these variables were frequently not considered. For these reasons, and because only one-hour and four-hour urine collections were needed, the methods of Johnson and his co-workers[5, 9] were adopted.

In 1945 Johnson and his associates[5, 9] established a simplified method of estimating the nutritional status of troops. A one-hour fasting morning sample was obtained; a test or load dose of thiamine (5 mg.), riboflavin (5 mg.) and nicotinamide (50 mg.) was given orally, and a four-hour specimen of urine was collected. Table 1 shows a comparison of the normal values for young, active, healthy

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troops in a temperate climate with those indicating tissue deficiency.

In the series of Johnson et al. it was not unusual to find a low fasting excretion and a normal load response, or vice versa. The only significant finding was a low fasting *and* a low load specimen. In this comprehensive study the correlation between the impression gained from the history, physical and urinary levels was unusually constant.

TABLE 1. *Excretion of Components of the Vitamin B Complex in Normal Subjects and in Patients with Tissue Deficiency.*

DOSE	THIAMINE EXCRETION		RIBOFLAVIN EXCRETION		NICOTINIC ACID EXCRETION	
	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN
	microgm.	*microgm.*	*microgm.*	*microgm.*	*microgm.*	*microgm.*
Healthy, active troops:						
Fasting	1 to 9 per hr.	4 per hr.	12 to 120 per hr.	35 per hr.	50 to 850 per hr.	300 per hr.
Load	40 to 450 per 4 hr.	150 per 4 hr.	1,165 to 3,820 per 4 hr.	2,155 per 4 hr.	250 to 11,000 per 4 hr.	3,750 per 4 hr.
Patients with tissue deficiency:						
Fasting	0.6 or less per hr.*		12 or less per hr.*		30 or less per hr.*	
Load	20 or less per 4 hr.*		200 or less per 4 hr.*		500 or less per 4 hr.*	

*Total values.

CHEMICAL METHODS

The methods employed were identical to those used by Johnson and his co-workers.[10] Thiamine is determined in its free form by conversion to a fluorescent thiochrome that can be colorimetrically compared to standards.

Riboflavin is similarly measured by Najjar's[11] method using a pyridine and acetic acid mixture, followed by potassium permanganate and hydrogen peroxide, the fluorescent solution being extracted, cleared and read fluorometrically.

In the normal urine the presence of various pyridine substances complicates the determination of urinary nicotinic acid.[12, 13] For this reason the method of Najjar and Wood[14, 15] was used. It is based on the principle that nicotinic acid is excreted proportionately to a fluorescent substance found in the urine after absorption with zeolite, elution with potassium chloride and alkalinization with sodium hydroxide. By quantitative measurement of the fluorescent factor (F_2), the relative values of nicotinic acid can be determined. The results are reported in micrograms of F_2 excreted in a given time, and not as nicotinic acid excretion.

CLINICAL MATERIAL

The present investigation undertaken with rheumatoid patients followed the established procedure of Johnson et al.[10] whereby one-hour fasting urine collections were made, after which a vitamin load was given and a four-hour collection taken. The 40 patients included in the series all had symptoms and signs of rheumatoid arthritis in varying stages. There were 16 males and 24 females. The ages ranged from thirteen to sixty-five, and the degree of activity varied from the mildest cases in the first attack to severe and long-standing cases. All patients upon entry to the hospital were questioned about the previous use of vitamin supplements, and a dietary history was taken. The influence of the previous home diet was minimized, since all patients in the study were on the hospital diet for

TABLE 2. *Fasting and Load Determinations in Patients with Arthritis and in Controls.*

DETERMINATION	THIAMINE EXCRETION OF CONTROLS		THIAMINE EXCRETION OF PATIENTS		RIBOFLAVIN EXCRETION OF CONTROLS	
	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN
	microgm.	*microgm.*	*microgm.*	*microgm.*	*microgm.*	*microgm.*
Standardization period						
Group I and II combined*:						
Fasting	1 to 12 per hr.	6.8 per hr.	1 to 20 per hr.	7.6 per hr.	10 to 123 per hr.	42 per hr.
Load	138 to 1,100 per 4 hr.	380.0 per 4 hr.	125 to 780 per 4 hr.	310.0 per 4 hr.	2,600 to 5,200 per 4 hr.	3,225 per 4 hr.
Vitamin period						
Group I†:						
Fasting			12 to 155 per hr.	60.0 per hr.		
Load			700 to 5,900 per 4 hr.	1,200 per 4 hr.		
Group II‡:						
Fasting	5 to 38 per hr.	24.0 per hr.	20 to 50 per hr.	34.0 per hr.	73 to 514 per hr.	118 per hr.
Load	300 to 2,500 per 4 hr.	819.0 per 4 hr.	600 to 1,400 per 4 hr.	864.0 per 4 hr.	4,200 to 7,800 per 4 hr.	5,474 per 4 hr.
Post-vitamin period						
Group II§:						
Fasting	2 to 11 per hr.	6.0 per hr.	1 to 53 per hr.	14.0 per hr.	25 to 55 per hr.	46 per hr.
Load	50 to 250 per 4 hr.	134.0 per 4 hr.	78 to 400 per 4 hr.	230.0 per 4 hr.	500 to 3,000 per 4 hr.	2,060 per 4 hr.

*40 patients and 6 controls over period of 14 to 40 days.

†26 patients (no controls) given 1 Vigran capsule for 30 days.

‡14 patients and 6 controls given 1 Vigran capsule for 10 days.

§14 patients and 6 controls over period of 14 days.

at least three weeks before being tested. The average daily diet contained: 2100 calories, 90 gm. of protein, 240 gm. of carbohydrate, and 85 gm. of fat, with 1.7 mg. of thiamine, 2.8 mg. of riboflavin, and 15.7 mg. of nicotinic acid.

The procedure for testing was as follows. Patients fasted during the night, voiding in the morning, and a fasting one-hour specimen was collected. Three such fasting specimens were collected at weekly intervals, and the average served as a base line. After the collection of the third fasting sample, a vitamin load was given that was a specially prepared solution* containing 5 mg. each of thiamine and riboflavin, and 50 milligrams of N-methylnicotinamide chloride; breakfast was eaten, and a four-hour urine specimen was collected for the load sample. Aliquots of each collection were tested as previously described without time for deterioration.

Two groups of patients and one group of controls were studied. The first group of 26 patients had repeated fasting and load measurements during a forty-day period of standardization. They were then placed on a vitamin supplement of one Vigran capsule (2 mg. of thiamine, 2 mg. of riboflavin, 20 mg. of nicotinamide, 0.5 mg. of pyridoxine, 1.0 mg. of calcium pantothenate, 5000 units of vitamin A, 45 mg. of vitamin C and 500 units of vitamin D) per day for thirty days, load and fasting tests being done at the end of this period. There were no controls with this group.

The second group of 14 patients and 6 controls had repeated fasting and load determinations during a two-week period of standardization. They then had one Vigran capsule per day for ten days, fasting and load tests being done at the end of this time. This was followed by a two-week period without supplement, and the tests were repeated. The 6 controls followed the same program and ate the same diet as the patients. A summary of the results is shown in Table 2.

*These substances were supplied for this study by the courtesy of Dr. D. F. Robertson, associate medical director, Merck and Company, Incorporated, Rahway, New Jersey.

Discussion

Before any conclusions can be drawn certain facts should be considered. The utilization of vitamin B depends on many circumstances, among them being caloric intake, muscular activity and the physical status of the organism. The controls were healthy, young, active adults who undoubtedly had a higher daily caloric intake and energy output than the patients. This makes it difficult to draw conclusions from any abnormalities of excretion that might be seen. Another point of importance is that the urinary excretion of vitamins or their by-products fluctuates widely throughout the day and from day to day. Thus, the results and the averages that are reported are merely an over-all picture of the amount of vitamins excreted by patients and controls.

In spite of these shortcomings, certain results are evident. First of all, no patient fell into the deficiency zones established for thiamine, riboflavin and nicotinic acid. Secondly, there was no correlation between the duration or the severity of the rheumatoid arthritis and the urinary excretions. Thirdly, the excretion figures for thiamine, riboflavin and nicotinic acid excretion (as measured by the F_2 factor) were comparable for patients and controls during the entire experiment.

Table 2 (*Concluded*).

Determination	Riboflavin Excretion of Patients		Nicotinic Acid (F_2) Excretion of Controls		Nicotinic Acid (F_2) Excretion of Patients	
	Range	Mean	Range	Mean	Range	Mean
	microgm.	*microgm.*	*microgm.*	*microgm.*	*microgm.*	*microgm.*
Standardization period						
Group I and II combined*:						
Fasting	12 to 81 per hr.	40 per hr.	230 to 1,200 per hr.	600 per hr.	200 to 2,000 per hr.	550 per hr.
Load	1,300 to 4,300 per 4 hr.	2,450 per 4 hr.	7,000 to 15,000 per 4 hr.	9,300 per 4 hr.	3,000 to 15,000 per 4 hr.	8,900 per 4 hr.
Vitamin period						
Group I†:						
Fasting	23 to 360 per hr.	65 per hr.			160 to 1,800 per hr.	510 per hr.
Load	1,400 to 15,700 per 4 hr.	3,500 per 4 hr.			2,000 to 50,000 per 4 hr.	19,500 per 4 hr.
Group II‡						
Fasting	30 to 320 per hr.	100 per hr.	200 to 1,300 per hr.	650 per hr.	500 to 1,600 per hr.	630 per hr.
Load	3,800 to 6,900 per 4 hr.	5,050 per 4 hr.	12,000 to 25,000 per 4 hr.	19,000 per 4 hr.	5,000 to 38,000 per 4 hr.	16,000 per 4 hr.
Post-vitamin period						
Group II§:						
Fasting	14 to 70 per hr.	38 per hr.	200 to 1,900 per hr.	600 per hr.	200 to 2,000 per hr.	730 per hr.
Load	500 to 4,800 per 4 hr.	2,400 per 4 hr.	2,500 to 13,000 per 4 hr.	6,300 per 4 hr.	4,000 to 17,000 per 4 hr.	9,000 per 4 hr.

Summary

A brief discussion of the historical background of vitamin B studies in arthritis is presented.

Fasting and load excretions of vitamin B in the urine are discussed, along with the chemical methods of measuring the amounts of thiamine, riboflavin and the F_2 substance for nicotinic acid.

The program of clinical investigation, using a period of standardization, vitamin supplement and follow-up study, is outlined.

It is concluded that arthritic patients on a normal hospital diet showed excretion levels of thiamine, riboflavin and nicotinic acid above the established deficiency levels and closely resembling the excretions of normal controls.

When supplementary doses of vitamin B were given there was no essential difference between the patients and the controls.

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MEDICAL PROGRESS

PHEOCHROMOCYTOMA*

A Discussion of Symptoms, Signs and Procedures of Diagnostic Value

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PHEOCHROMOCYTOMAS are rare tumors that may cause any known form of hypertension. Although the hypertension may be and most commonly is paroxysmal, it may also be nonparoxysmal. In either case, the hypertension may be intermittent or persistent. Pheochromocytomas develop from chromaffin tissue and consequently are found wherever this occurs. The most common location is the medullary portion of the adrenal gland. Tumors also arise from sympathetic-ganglion tissue and consequently may be found in various locations. The most common site of origin other than the adrenal gland is the organ of Zuckerkandl, which is located just above the aortic bifurcation. In somewhat less than 20 per cent of cases there may be two tumors. Under these circumstances they are most likely to arise from both adrenal glands or from the medulla of one and the organ of Zuckerkandl. Other combinations of locations have been reported in a few patients. The tumor is situated in the lumbar region in about 5 per cent of cases and in unusual locations, mostly within the abdominal cavity, in another 5 per cent. In 3 cases, the tumors were intrathoracic and in 1, intracranial in position. For some unknown reason, the right adrenal gland was involved almost twice as frequently as the left in the cases we have reviewed.

It is apparent from the increasing frequency of case reports in the literature that physicians are becoming more aware of the possible existence of this tumor. It is well that this is so because the aspect of the problem that needs greatest emphasis is diagnosis, for if the condition is recognized before irreversible cardiovascular damage or sudden death results, the outcome of successful removal is almost invariably dramatic. A study of representative collective reviews of this subject indicates that from the time of the earliest recognition of the tumor to the present, it has been principally an autopsy diagnosis[1] (Table 1).

The stimulus for this report is an experience with 11 cases. In most of these, the diagnosis was not made prior to operation. The tumors were found during the course of the routine inspection and palpation of the adrenal glands that is carried out in all patients undergoing splanchnicectomy for hypertensive cardiovascular disease. In 3 cases the diagnosis was either made or strongly suspected prior to operation. Operation was not performed in one case in which the diagnosis was obvious be-

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cause the patient was in the terminal stage of hypertensive cardiovascular disease on admission to the hospital.

We have reviewed the data available on our patients and have also studied 107 case reports in the literature in detail with a view toward clarifying the diagnosis. Particular emphasis is placed upon symptoms and signs and on diagnostic procedures that are safe and available to every physician. For comparison, the relative frequency of the symptoms, signs and positive findings among 100 consecutive unselected cases of so-called essential hypertension are included. These data are arranged according to the frequency observed in our own cases and are presented in Table 2.

TABLE 1. *Incidence of Pheochromocytomas Proved at Operation and at Autopsy.*

AUTHOR	DATE	NO. OF CASES COLLECTED FROM LITERATURE	CASES PROVED AT OPERATION	CASES PROVED AT AUTOPSY
			%	%
MacKenzie and McEachern[2]	1938	82	24	76
MacKeith[3]	1944	165	22	78
Smithwick et al.[1]	1949	270	33	67

EXCESSIVE SWEATING

A high percentage of patients with pheochromocytoma complain of excessive sweating. This applies to those who do not have paroxysmal attacks as well as to those who do. In the first group, the patients may not comment upon this symptom and must be specifically questioned about it. The sweating is usually generalized in distribution. Since sweat glands are innervated by cholinergic nerves it is obvious that the excessive sweating is not due to the action of epinephrine upon the neuroeffector mechanism. It is presumably an indirect effect of epinephrine resulting from the stimulation of parasympathetic centers in an attempt to maintain homeostasis, body temperature in particular. Excessive sweating is generally noted at the end of a paroxysmal attack. The sudden outpouring of epinephrine causes increased body temperature because of increased heat production (calorigenic effect) as well as interference with heat elimination due to peripheral vasoconstriction. This presumably results in increased parasympathetic outflow from the midbrain, with resulting drenching perspiration that tends to lower body temperature. Excessive perspiration is rarely noted as a symptom by patients with essential or malignant hypertension. By contrast, excessive sweating was noted in 9 out of 10 of our cases. The other patient was not questioned on this point. This symptom was mentioned in 52 per cent of the case reports in the literature that we have reviewed (Table 2).

PERIPHERAL VASOMOTOR PHENOMENA

Epinephrine causes constriction of the cutaneous arterioles, and as a consequence the circulation to the body surface is reduced. Evidence of this is reduced skin temperatures and blood flow. Under certain circumstances, curiously enough, increased blood flow to the extremities was noted in some of our patients. We suspect that this occurs during a phase of reaction to the increased outpouring of epinephrine and is probably associated with an increased basal metabolic rate and perhaps elevated body temperature. For the most part, sporadic evidences of vasoconstriction, such as coldness of hands and feet, blanching of fingers and mottled, bluish-red discoloration of the legs or hands, are noted by a high percentage of patients with pheochromocytoma. Numbness and tingling of the extremities may be present at times. During paroxysmal attacks the skin temperature has been observed to fall materially (10 to 15°F.),[4] and this may be associated with marked pallor. During severe and prolonged attacks the peripheral pulses may actually disappear, and constriction of the retinal arteries has been noted. Evidence of vasoconstriction such as those commented upon are rarely noted by patients with essential hypertension, although rare patients appear to have Raynaud's phenomena in association with hypertension. In general, peripheral vasomotor phenomena in hypertensive patients should lead one to suspect the presence of a pheochromocytoma. As with excessive sweating, one must specifically question the patients for evidence of peripheral vasoconstriction, since they may not comment upon these signs and symptoms spontaneously. These were mentioned in 50 of the 107 case histories in the literature and in 9 of 10 of our cases (Table 2).

TABLE 2. *Symptoms Signs and Findings Suggestive of Pheochromocytoma.*

SYMPTOMS, SIGNS AND FINDINGS	INCIDENCE AMONG 11 PHEOCHROMOCYTOMAS IN PRESENT SERIES	INCIDENCE AMONG 107 PHEOCHROMOCYTOMAS IN LITERATURE	INCIDENCE AMONG 100 CASES OF ESSENTIAL HYPERTENSION
	%	%	%
Excessive sweating	90	52	2
Vasomotor phenomena	90	47	0
Elevated temperature	78	70	10
Normal cold-pressor response	73	63	22
Fasting blood sugar of 120 mg. per 100 cc. or more	64	61	13
Basal metabolic rate of +20 per cent or more	60	57	5
Postural tachycardia	55	—	15
Postural hypotension	44	50	3
Glycosuria	36	50	4
Paroxysmal attacks	36	75	0

Elevated Body Temperature

We were surprised to find that in 73 per cent of our patients and in 70 per cent of the case reports that we studied in which the observation was recorded, unexplained elevations of body temperature (1°F. or more) were noted. This finding has not been sufficiently emphasized in connection with the diagnosis of pheochromocytoma. The elevation of temperature is readily explained by interference with heat elimination due to peripheral vasoconstriction as well as by increased caloric output caused by epinephrine. It may occur in patients with essential hypertension but far less frequently. The elevations that were noted in our cases of pheochromocytoma were sporadic and not necessarily related to paroxysmal symptoms. During paroxysmal attacks, the body temperature may rise to 105°F. It seems advisable to obtain frequent rectal temperatures in hypertensive patients over a forty-eight-hour period. Unexplained elevations should lead one to suspect the presence of a pheochromocytoma and to search for confirmatory evidence.

Normal Cold-Pressor Response

In 1932 Hines and Brown[5] described the cold-pressor test and indicated that the great majority of hypertensive patients responded to the immersion of one hand in ice water for one minute by an excessive rise in blood pressure. After studying the response of both normal and hypertensive patients to this stimulus the authors concluded that a rise of over 20 mm. in the systolic and 15 mm. in the diastolic pressure was abnormal. About 15 per cent of normal persons respond abnormally, and over 90 per cent of their hypertensive patients did likewise. It is important that this observation be made under resting conditions because in hypertensive patients in particular, who respond to many stimuli, if the patient has already been stimulated by emotion or unsatisfactory conditions of study, a further response to exposure to cold may not be elicited. For many years, we have included the cold-pressor test, carried out under resting conditions in a quiet environment, as part of the study of blood pressure in hypertensive patients.[6] As indicated by Table 2, a normal response to cold is decidedly the exception in patients with essential hypertension. It is commonly observed in patients with pheochromocytomas. Of our patients, 7 of 9 (78 per cent) had a normal cold-pressor response. This test was performed in only 11 of the 107 cases we reviewed. The response was normal in 63 per cent of these patients. It is apparent, therefore, that a normal response to cold in a hypertensive patient is unusual and should cause one to consider the possible presence of a pheochromocytoma.

Fasting Blood Sugar of 120 mg. Per 100 cc. or More

Epinephrine causes the mobilization of preformed carbohydrate stored in the liver and muscles. It is therefore not surprising that evidence of elevation of blood sugar levels may be noted rather frequently in patients with pheochromocytoma. This may be a persistent finding and when combined with glycosuria and a diabetic type of glucose-tolerance curve may lead to the erroneous diagnosis of diabetes mellitus. As with body-temperature elevation, increased sweating, peripheral vasomotor phenomena and increased metabolic rate, the elevation of blood sugar may not be constantly present and may vary in magnitude. A fasting blood sugar as high as 400 mg. per 100 cc. has been noted in the presence of a pheochromocytoma.[7] Elevated levels occur both in paroxysmal and nonparoxysmal forms of the disorder. In 7 of our 11 cases (64 per cent) the blood sugar on one or more occasions was 120 mg. per 100 cc. or more. Fasting blood sugar levels, which were recorded in less than half the 107 case reports reviewed, were elevated in 61 per cent. Levels of 120 mg. per 100 cc. or more were noted in 13 of 100 consecutive cases of essential hypertension. It is apparent, therefore, that elevated blood sugar levels in hypertensive patients should make one consider the possible presence of a pheochromocytoma. Such patients have been treated as if they had diabetes and may respond in the usual manner or may be resistant to insulin. When the tumor is removed, the blood sugar falls to normal, the glucose-tolerance curve changes from the diabetic type to or toward normal, and glycosuria disappears.

Basal Metabolic Rate of +20 Per Cent or More

Elevated basal metabolic rates have been reported in patients with essential hypertension. Occasionally, the level is quite high. Of 100 consecutive cases, 5 per cent of patients had levels of +20 per cent or more. In our cases of pheochromocytoma the basal metabolism was studied on one or more occasions in 5 patients. In 3, the rate was +20 per cent or more. Of the 107 case reports studied, the metabolic rate was determined in 35 and was elevated in 57 per cent. The rate may fluctuate considerably, depending upon variations in output of epinephrine. In 1 of our cases the rate varied from +1 to +74 per cent. In another, it ranged from +22 to +142 per cent. This type of hypermetabolism is refractory to thyroidectomy, and to the action of the various antithyroid drugs.[1] A basal metabolic rate of +20 per cent or more in a hypertensive patient should arouse suspicion, and should make one search for other evidence of the presence of a pheochromocytoma.

Postural Tachycardia and Postural Hypotension

In addition to the cold-pressor test, it has been our custom for many years to study the effect of change of posture upon the pulse rate and blood pressure of hypertensive patients.[6] We were particularly interested in the manner in which blood pressure and pulse rate might be affected by the various operations upon the sympathetic nervous system that have been under study in the treatment of essential and malignant hypertension. To obtain data on this point a simple postural blood-pressure test has been performed in which, after a period of rest in the horizontal position, blood pressure and pulse rates are recorded every minute for five minutes, with the patient recumbent, sitting and standing. It is most unusual for both the systolic and diastolic pressures in the upright position to fall below the levels observed in the horizontal position in ordinary hypertensive patients. Also, a rise in pulse rate (average of the five determinations) of 20 beats per minute or more when the patient is standing above that noted when he is lying is very unusual in such cases. These observations were made in 9 of our 11 cases of pheochromocytoma. Five (55 per cent) showed postural tachycardia, and 4 (44 per cent) showed postural hypotension. All the latter had postural tachycardia as well. Among patients with essential hypertension, 15 per cent show postural tachycardia, and 3 per cent postural hypotension. Among the 107 cases of pheochromocytoma reviewed, the effect of posture upon pulse rate was not recorded in a single case. The effect of posture upon blood pressure was recorded in 2 cases, and, in 1 of these, postural hypotension was noted. To illustrate these changes as well as the lack of an abnormal response to cold, a postural and cold blood-pressure test performed prior to operation upon a patient with persistent hypertension of the nonparoxysmal type due to a pheochromocytoma is shown in Figure 1. For comparison, a postural and cold blood-pressure test performed in a typical case of essential hypertension is illustrated in Figure 2. The difference in the effect of posture on pulse rate and blood pressure as well as the blood-pressure response to cold in the horizontal position is very striking. It seems probable that the effect of posture on pulse rate and blood pressure will be noted principally in patients with persistent hypertension due to pheochromocytoma. In patients with normal blood-pressure levels between attacks, these changes presumably would not be present. The explanation for these phenomena is not known. It seems probable that they are due to decreased venous return to the heart in the upright position and may be related to alterations in blood flow such as splanchnic and muscular vasodilatation of humoral origin, which takes precedence over the normal vasoconstrictor mechanisms involving the autonomic nervous system that are called into play when one assumes the

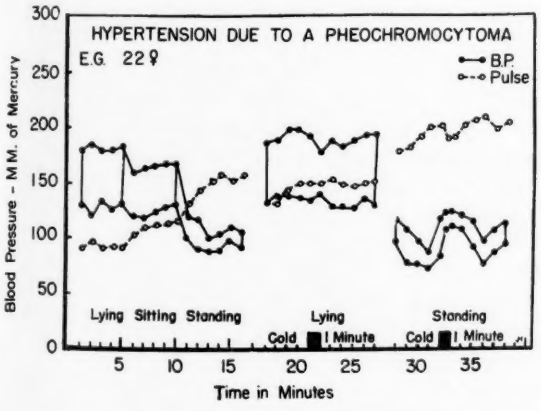

Figure 1. *Blood Pressures and Pulse Rates during a Routine Postural and Cold Test in a Twenty-Two-Year-Old Woman with a Persistent Nonparoxysmal Form of Hypertension Due to a Pheochromocytoma.*

Note the marked postural hypotension and tachycardia, and also the lack of response to cold in both the horizontal and the upright position. These findings are in sharp contrast to those shown in Figure 2. The values for blood pressure are 181/127 in the recumbent and 109/92 in the standing position, the pulse rates being 93 and 149 respectively. The response to cold is indicated by blood pressures of −14/+2 in the recumbent and +8/+20 in the standing position.

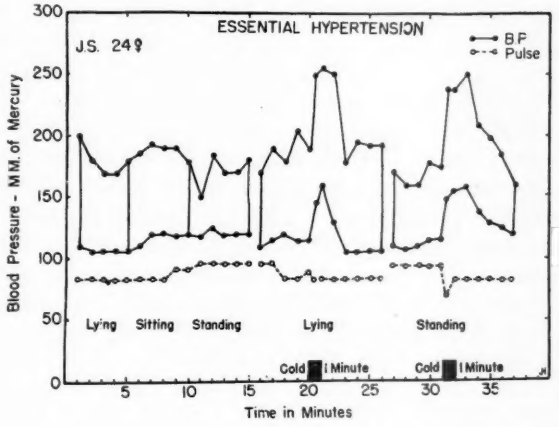

Figure 2. *Blood Pressure and Pulse Rate as Determined by a Routine Postural and Cold Test Performed upon a Twenty-Four-Year-Old Woman with Essential Hypertension.*

Note that there is little difference between the blood-pressure level in the recumbent and that in the standing position (average of the five readings in each position). The pulse rate increases less than 20 beats on standing. There is a marked response to cold in both the horizontal and the upright position. These findings are characteristic of the majority of patients with essential hypertension. The values for blood pressure are 179/107 in the recumbent and 172/121 in the standing position, the pulse rates being 84 and 96 respectively. The response to cold is indicated by blood pressures of +66/+44 in the recumbent and +62/+40 in the standing position.

upright position. A reduction of both systolic and diastolic pressure, however slight, when the subject assumes the erect position should cause one to suspect the presence of a pheochromocytoma, particularly when associated with an unusual rise in pulse rate and a normal blood-pressure response to the cold-pressor test.

Glycosuria

Glycosuria was noted in 4 of 11 (36 per cent) of our cases of pheochromocytoma. This was noted both in the presence and in the absence of elevated blood sugar levels. Glycosuria was present in only 4 per cent of 100 cases of essential hypertension. Of the 107 case reports reviewed, glycosuria existed in 50 per cent of those in which the presence or absence of this finding was recorded. This is simply another evidence of disturbed carbohydrate metabolism and an additional finding that should cause one to suspect the presence of a pheochromocytoma. It is of interest that elevated blood sugar levels were noted more frequently than glycosuria in our patients.

Paroxysmal Attacks

Paroxysmal attacks of hypertension associated with certain symptoms have generally come to be regarded as characteristic of a pheochromocytoma. Although the majority (75 per cent) of the patients in the cases reviewed had such episodes, it seems important to emphasize that the other patients had no such attacks and that they were present in only 36 per cent of our small series of cases. When present, such attacks must be regarded as very suggestive of the presence of a pheochromocytoma. It should be understood, however, that a very definite percentage of these patients will not have the attacks, and consequently one must depend for a diagnosis upon the other criteria discussed. It should also be pointed out that some patients have severe attacks of paroxysmal hypertension associated with the symptoms characteristic of a pheochromocytoma without such a tumor. We have had a number of these cases, and they may be very difficult to differentiate from the tumor group. The attacks are presumably due to outbursts of diencephalic activity whose precipitating cause is unknown.[8] The hypertension in these cases is probably neurogenic. So far, all the patients of this sort that we have studied have been hyperreactors to cold. They have all responded well to splanchnicectomy. In paroxysmal hypertension due to a pheochromocytoma, the blood-pressure levels may be either normal or elevated between attacks. The attacks may last a few minutes or several hours. In general, they are infrequent at first, but with the passage of time occur more often, occasionally many times a day. They may be precipitated by pressure over the tumor, straining, lying in certain positions and emotion. The most commonly associated symptoms noted during these attacks are headache, palpitation, pain in the abdomen, chest, back or extremities, nausea or vomiting, drenching sweats and exhaustion.

Supplementary Studies of Diagnostic Value

We have purposely emphasized certain signs, symptoms and procedures as aids in the diagnosis of pheochromocytoma because they can easily be obtained by any physician in the routine study of hypertensive patients. It is our belief that if these data were regularly available, one would rarely fail to consider the diagnosis. We suspect that in every case of pheochromocytoma at least three or four of the findings referred to would be present, and that in some a majority would be noted. In most cases, the diagnosis would usually be clear and would warrant surgical exploration without further study.

However, a number of other studies may be utilized as further confirmation of the diagnosis, and these are as follows:

X-Ray Examinations

Intravenous pyelograms were obtained in 10 of our 11 cases and were normal in 9. This is due to the fact that most of the tumors are small, 3 or 4 cm. in diameter, and cause no displacement of the kidney. If the tumor is larger, it will depress the upper pole of the kidney and cause it to be displaced laterally. Generally speaking, intravenous pyelograms should be obtained routinely in the study of hypertensive patients. Negative studies do not exclude the presence of a pheochromocytoma. In 1 of our cases, the tumor was demonstrated by means of a laminogram. Air may be injected in the perirenal area. This is generally not regarded as an innocuous procedure. It has resulted in sudden death due to air embolism, and in false-negative and false-positive diagnoses. Although this test has confirmed the diagnosis in some cases, it seems wiser to pay greater attention to other diagnostic aids.

Glucose-Tolerance Test

Glucose-tolerance curves are usually of the diabetic type and should be performed in the presence of hypertension associated with elevated blood sugar or glycosuria. After removal of the tumor, the curves reverted to or toward normal in our patients.

Precipitation of Attacks

In 1945 Roth and Kvale[9] reported the interesting observation that the injection of histamine precipitated a typical attack of hypertension in a patient with a pheochromocytoma. They have recently summarized their experiences with the use of histamine as a diagnostic measure.[10] More recently, it has been noted that other drugs will precipitate attacks. These have followed the use of methacholine chloride[11] and tetraethylammonium bromide.[12] The mechanism by which these attacks

are precipitated is not known. It is possible that reflex stimulation of the adrenal gland is brought about through the carotid sinus in response to a transient preliminary fall in blood pressure. These drugs may give both false-negative and false-positive results. The response may be very severe and may result in fatal or nearly fatal complications. It is probably reasonably safe to use them in patients with normal blood pressures between attacks, but it is hazardous to use them in patients with high levels between attacks or in nonparoxysmal forms of sustained hypertension. In any event one should always be prepared to administer an epinephrine-blocking agent to terminate the attack promptly should alarming signs and symptoms appear.

Use of Blocking Drugs

An increasing number of drugs that have the capacity to block the action of epinephrine are coming into use.[13, 14] On the whole, they appear to be safer and will probably be of value both in the diagnosis and in the operative management of these patients. It should be stated, however, that alarming reactions have been noted in some of our tumor suspects who have been given these drugs and who had severe hypertensive cardiovascular disease without a tumor. It is to be hoped that these preparations will be helpful in the diagnosis of pheochromocytoma in the presence of nonparoxysmal persistent hypertension. It is also to be hoped that blocking agents will prove effective in preventing severe exacerbations of hypertension during operation. It seems desirable to use a drug of short rather than long action, particularly during operation upon patients with persistently high blood-pressure levels, since these patients are likely to go into profound shock the moment the tumor is removed. Both types of drugs have been used.[14, 15] Intravenous injection of epinephrine has been the most effective therapy so far available for combating shock after removal of a tumor. If a long-acting drug, which would have blocked the action of injected epinephrine, had been administered, the result might have been disastrous. Much more experience and study is needed before this aspect of the matter can be discussed in detail.

Summary

The need for greater accuracy in the diagnosis of pheochromocytoma is stressed. Certain signs, symptoms and findings that should be helpful in leading physicians to suspect the presence of this tumor are enumerated.

Specifically, attention is directed to the importance of excessive perspiration, vasomotor phenomena, a normal cold-pressor response, elevations of temperature, blood sugar and basal metabolic rate, postural tachycardia, postural hypotension, glycosuria and paroxysmal attacks of hypertension.

It is believed that if these data are obtained regularly in the study of hypertensive patients, the diagnosis of pheochromocytoma will rarely be overlooked. The data stressed are readily available to any physician and require no unusual facilities.

Certain supplementary diagnostic procedures are commented upon briefly.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 36071

PRESENTATION OF CASE

A twenty-seven-year-old housewife entered the hospital because of recurrent episodes of hemoptysis.

For eight years before admission the patient had repeated hemoptyses of varying degree, usually following overexertion or upper respiratory infection. For the most part, these consisted of the expectoration of slight to moderate amounts of blood mixed with sputum over a period of several days. The first change in the severity of incidents occurred a little over three and a half years before admission when, after playing ball, the patient coughed up some pure blood. One year later she "vomited" a cupful of blood and entered the hospital for four days. X-ray films here showed increased pulmonary vascular markings and large hilar vessels with apparently slight enlargement of the left auricle. There was calcium in the region of the mitral valve, but the heart was not enlarged. Following discharge small hemoptyses continued to occur over periods of several days once or twice a month, usually after strenuous exercise. Four weeks before the present admission a head cold developed and spread to the chest, causing vigorous coughing. Two weeks preceding entry there was a series of four daily hemoptyses designated "severe" by the patient, and on another day there were three slight episodes of bleeding. During the subsequent week she had only a small amount of fresh blood in the mouth each morning. It was always bright red and mixed with sputum. One week before admission, fleeting pains were experienced in the knees, elbows and hands lasting only a few hours and not associated with redness, swelling or tenderness. No other episodes of joint pain had occurred during the years of the present illness. There had been no dyspnea, fatigue, fever, sweating, palpitation, ankle edema or weight change.

As a child, the patient suffered frequently from severe migratory joint pains but was never incapacitated by them. She had always had a heart murmur and knew definitely that it was present at the age of three years, when she had measles and pneumonia. In general she had always led a vigorous, happy life without symptoms referable to the heart. Two years before the present admission she was in the hospital for three days because of acute, diffuse abdominal pain and tenderness, which were not associated with fever or leukocytosis and which cleared spontaneously.

On physical examination the abnormal findings were limited to the heart and lungs. The left cardiac border was percussed 10.5 cm. to the left of the midsternal line. The heart beat was regular. The pulmonic second sound was loud and snapping. A loud presystolic murmur heard at the apex was not transmitted. (In the first admission two and a half years previously a different observer had described a loud "systolic" apical murmur.) There

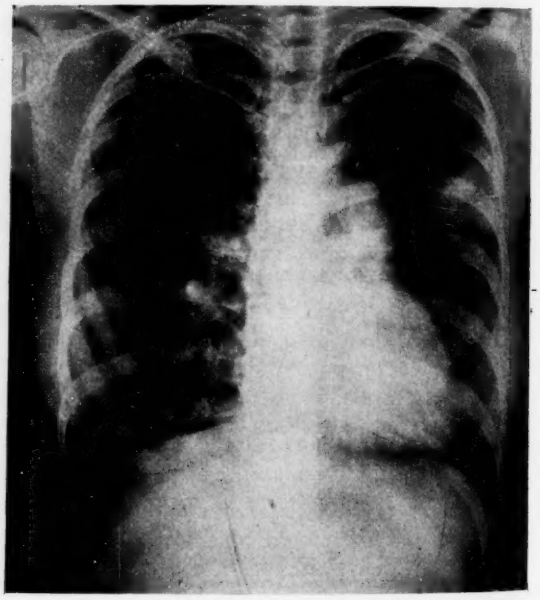

FIGURE 1.

were moist rales at both lung bases, more on the left. No edema, dyspnea, liver enlargement, venous engorgement or joint involvement was noted.

The temperature was 98.6°F., the pulse 70, and the respirations 18. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood disclosed a hemoglobin of 14.9 gm. and a white-cell count of 6900. The erythrocyte sedimentation rate was 7 mm. in sixty minutes. X-ray examination of the chest showed an area of increased density in the left-lateral-lung field underlying the left third rib and third interspace (Fig. 1). In the lateral projection it

was seen to lie in the axillary line. The margin of the area was not sharply demarcated. The remaining lung fields were clear except for prominent vascular markings, which on comparison with films taken two and a half years previously had not changed materially. Both hilar shadows were prominent, apparently from slightly dilated pulmonary vessels. The heart still showed prominence in the region of the pulmonary arteries. In the overexposed grid film a shadow consistent with a calcified mitral valve was seen.

In the hospital the patient was well except for slight blood spitting. She never suffered from fever or chills. At bronchoscopy the left main bronchus contained a small amount of old blood. The left-upper-lobe orifice appeared almost completely blocked by dark blood clot. Her condition remained unchanged, and on the sixteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Howard B. Sprague*: When I started to read this case I thought that the Pathology Department had become kind for a change and given me an easy case, until the "punch" line at the end of the history — "an operation was performed." I do not see how one can escape the diagnosis of rheumatic heart disease with mitral stenosis. To begin with, it is practically an exhortation on the part of the historian that we make this diagnosis of mitral stenosis. We have a young woman with a history of severe recurrent joint pains in childhood with a murmur since the age of three, slightly enlarged left auricle, increased vascular markings, loud pulmonic second sound, presystolic murmur, calcium in the region of the mitral valve and repeated hemoptyses for eight years. It would be hard to get me away from a diagnosis of mitral stenosis. I once made the diagnosis of mitral stenosis in a patient who turned out to have myxoma of the auricle, so that I know there are other conditions that simulate it. But that patient did not have calcium in the region of the mitral valve, or all the rest of the findings described here.

The hemoptysis was related characteristically to effort or upper respiratory infection, and the present attack was brought on by a cold, with a cough a month previously, followed in three weeks by what seems to have been a mild reactivation of rheumatism with joint pains but no fever, redness or swelling of the joints to go with it. Otherwise it is a classic description. Two years before entry there was an episode of abdominal pain and tenderness, but no fever or leukocytosis, for which I have no adequate explanation at the moment. One notes in this history the absence of chest pain or chronic cough between the episodes. She had no weight loss, dyspnea, cyanosis or signs of congestive failure except for the presence of basal rales. One might be satisfied by the old principle of diagnostic parsimony in young people and attempt to get everything into one diagnosis except for this x-ray picture of the lung.

We must consider causes of hemoptysis coming from the lung itself. We know that on bronchoscopy the hemorrhage was located below the upper air passages. Exclusive of mitral disease, one thinks first of tuberculosis. I do not know whether Dr. King saw this patient or not.

Dr. Donald S. King: Yes, I did.

Dr. Sprague: In a tuberculosis sanatorium patients are frequently seen with hemoptysis from unrecognized mitral stenosis. There is no statement about a sputum examination, but I assume if Dr. King saw the patient that she did not have tuberculosis unless he said so.

Regarding the question of neoplasm, it is hard for me to think of this as being a primary malignant neoplasm, in the absence of clinical symptoms in a young woman with a long story. It is true that occasional metastatic cancer can cause hemoptysis. We can consider later the possibility of benign processes. There is no reason to believe that the hemoptysis was due to repeated infarctions of the lung, congenital heart disease, foreign body or some bizarre infection of the lung, such as rheumatic pneumonia, or that it was the rare congenital hemoptysis that occurs in the textbooks.

May I see the x-ray film?

Dr. Stanley M. Wyman: This single film shows the area of density described in the left-lung field. It is hazy, very ill defined and very homogeneous. It suggests hemorrhage.

Dr. Sprague: Hemorrhage with attendant atelectasis. Is the heart displaced to the left?

Dr. Wyman: It might be a little. It shows the unusually prominent pulmonary artery and unusually prominent hilar vascular markings on both sides. The heart itself is not particularly enlarged in the anteroposterior view. The size is within normal limits.

Dr. Sprague: Would you be inclined to think that was tuberculosis?

Dr. Wyman: No.

Dr. Sprague: Would you vote against its being a tumor?

Dr. Wyman: Yes.

Dr. Edward F. Bland: Would you like to know about the electrocardiogram? It showed right-axis deviation.

Dr. Sprague: That is consistent with mitral stenosis.

It was stated that an operation was performed. I did not think that the operation performed was a mitral valvulotomy; I did not believe that a simple biopsy from bronchoscopy would be considered an operation; and I did not believe that it was a therapeutic pneumothorax, although pneumothorax has been tried unsuccessfully in the treat-

*Associate physician, Massachusetts General Hospital.

ment of angioma of the lung. I went to the extent of asking the Pathology Department if this operation revealed the diagnosis. I did not know whether the patient had died or not. I was told that the operation demonstrated the diagnosis, and then I was not quite sure whether that meant that a complete cardiac diagnosis was apparent from the operation or not, or whether it was clear that the patient had mitral stenosis, or whether this diagnosis was assumed. So I decided that probably the surgeons either tried to dissect something from the lung in this area or took the lobe of the lung out. I have always wondered why some patients with mitral stenosis seem to have more hemoptysis than others. It is true that one sees it in patients who apparently are otherwise fairly well. One wonders if it is associated with some congenital vascular abnormality in the pulmonary circulation that makes them more susceptible to hemorrhage in association with pulmonary hypertension from mitral disease. I wondered if by any chance the surgeons had decided that since they had localized the area from which this patient apparently was having hemorrhage, they would go ahead and actually take that area out. On the assumption that this was the area from which hemorrhage was coming, I had made up my mind that I probably would see x-ray films that showed hemorrhage and some atelectasis, and I did not know what the pulmonary surgeons might have been able to accomplish in a condition of this sort. I was hard put to understand just what this operation was. Certainly, the evidence was against a malignant process. On the other hand, could there have been a small lesion such as a hemangioma or an arteriovenous fistula that made the lung bleed easily? Could there have been anything in the peritoneal cavity in the nature of small hemangiomas that could have had any relation to the attack of abdominal pain from which she recovered? These x-ray shadows do not look like the nodules that come and go in polycythemia vera. I believe that is correct.

Dr. Wyman: Yes; nor is it the hemorrhage that might be seen in polycythemia.

Dr. Sprague: Was this patient relatively anemic? The hemoglobin was 14.9 gm., and she had a good deal of hemorrhage. Did she have a high red-cell count previously? That is very tenuous evidence. Could she have had an arteriovenous communication without observation of a murmur over this area? In any event I am still going to say that she had rheumatic heart disease with mitral stenosis, which caused the hemorrhage from the lung, and that there was sufficient localization of the hemorrhagic area so that a local operation was done, but I cannot rule out some minor congenital vascular abnormality in that part of the pulmonary tree.

Dr. Ronald C. Sniffen: What about the murmur at the age of three?

Dr. Sprague: We have seen rheumatic fever at that age at the House of the Good Samaritan. One can have an infection of the mitral valve at the age of three with slowly progressive mitral stenosis and the production of calcification at the age of twenty-seven, if it is true that that calcification was in the mitral valve.

Dr. King: I saw this patient only once and made a diagnosis of mitral stenosis and a questionable congenital heart defect and let it go at that. She was seen afterward by Dr. John Cass, and Dr. Sweet operated on her. I have nothing particular to suggest, but I think the comments by Dr. Paul White might be interesting, after Dr. Sweet has been heard from.

Dr. Edward B. Benedict: I did the bronchoscopy on this patient. We thought that repeated hemoptysis in a young woman over a long period spelled benign adenoma of the bronchus. We thought that before and after the bronchoscopy.

Dr. Richard H. Sweet: It was because of this fear that we decided to operate. We thought it was tumor and not tuberculosis or infarct. We operated for a tumor, possibly an adenoma, although the shadow that we see is too peripheral for the usual adenoma.

Clinical Diagnosis

Tumor of lung;? adenoma.

Dr. Sprague's Diagnoses

Rheumatic heart disease, with mitral stenosis.
Congenital vascular anomaly of left lung?
Pulmonary hemorrhage.

Anatomical Diagnoses

Congenital heart disease: persistent truncus arteriosus.
Pulmonary hemorrhage.

Pathological Discussion

Dr. Sweet: At operation it was obvious that there was a large lesion in the upper lobe. When we let the intratracheal pressure down, the mass stood out much like a tumor. It did not look like an infarct. I could not tell what it was. We decided to resect the upper lobe. I think it would be more helpful if I read my operative note:

> An incision was made across the left side of the chest and the sixth rib was resected. The lung was adherent. In the axillary segment of the upper lobe there was a brownish discoloration on the surface of the lung about 5 cm. in diameter. When the pressure in the bronchi was reduced by the anesthetist, this area was found to correspond with a tumor mass that stood up from the remaining surface of the lung. The dissection of the hilus was then begun in order to free the upper lobe, and it was soon recognized that there was something peculiar about the pulmonary artery. The first artery going to the upper lobe was in itself as large as an ordinary pulmonary artery. That was my first inkling that something peculiar was going on. It was soon recognized after careful dissection that there were four branches going to the upper lobe, all of which were unusually large, and the main pulmonary artery was more than twice the diameter of the

usual pulmonary artery and was fully as large as the usual descending portion of the aorta. A careful search was then made, and it was discovered that there was no pulmonary artery coming from the heart. The ventricles of the heart appeared to be rather small and rounded. The auriculoventricular cleft was easily identified. The ascending portion of the aorta was immense, fully twice the size of the ordinary aorta, and coming off this trunk just about at the apex of the aortic arch was the large pulmonary artery previously described. From the point where the pulmonary artery left the aorta, the aorta was very much diminished in diameter and about the size of a finger. The innominate artery and the left common carotid and subclavian arteries appeared to be about normal in diameter and came off in the usual location. There was no evidence of coarctation of the aorta.

Dr. Paul D. White happened to be in the hospital, came up to look at the condition and said that he had read about it but had never seen a case. It was he who suggested that the patient had a single-chambered ventricle with a double auricle.

Dr. Sniffen: From Dr. Sweet's description and his demonstration at the time of operation it is possible that this case is an example of persistent truncus arteriosus. With this anomaly there is always failure of development of the membranous interventricular septum and usually four valve cusps protect the common orifice. The pulmonary arteries arise from the truncus. Dr. Maude E. Abbott* illustrated several such cases in her atlas, but all the patients were cyanotic and only 1 lived to the age of this patient. With the evidence at hand one cannot be dogmatic. The lesion in the lung demonstrated by x-ray examination was 3 cm. in diameter and lay immediately beneath the pleura. It looked like a recent infarct and was sharply circumscribed. Microscopically, the air spaces were filled with blood, but unlike an infarct of this duration the alveolar walls were unaltered, and the capillaries were patent. No thrombus could be found in the pulmonary vessels. The large pulmonary arteries throughout the lobe showed atherosclerosis, and the walls of the arterioles were thickened. No other lesions were discovered.

Dr. King: Dr. White sent the x-ray films to Dr. Helen Taussig, at Johns Hopkins Hospital, who stated, "They are remarkable and from the contour of the heart I wonder whether she has truncus arteriosus combined with a single auricle and a single ventricle; certainly, she has increased hilar markings and adequate circulation to the lung."

Dr. Alfred Kranes: Is there any explanation for the hemoptysis?

Dr. Sniffen: I believe it was caused by pulmonary hypertension.

Dr. Kranes: Localized?

Dr. Sniffen: This particular lesion was localized, but she did have another hemoptysis three months after operation.

Addendum

This patient was operated on five years ago, and the above discussion presented. It was not published then because there was some doubt whether mitral stenosis may not have been present.

During this five-year interval she has been getting along very well doing housework, but avoiding strenuous exertion. She noticed no dyspnea, orthopnea, palpation or cyanosis. However, she has had three further episodes of bleeding, the first approximately three months after operation, the second one year after operation and the last three years after operation. She has recently been examined by Dr. Paul D. White, who made the following note:

> The heart is not enlarged, the left border of dullness being 7.5 cm. from the midsternal line. The sounds are of good quality, with the pulmonic second sound much accentuated. The mitral first sound is not accentuated. There is a Grade I pulmonary systolic murmur of somewhat rough quality and an apical blowing Grade I systolic murmur. No diastolic murmur is heard.
>
> She seems in first-rate condition, free of cyanosis and clubbing, and without any evidence whatsoever that I can find of mitral stenosis or rheumatic heart disease. However, she continues to have pulmonary hypertension. Whether that is due to the crowding of the pulmonary circulation by the volume of blood going from the right ventricle entirely into the right pulmonary artery or to some other condition I do not know, but the pulmonary hypertension undoubtedly accounts for the electrocardiographic evidence of right-axis deviation.

CASE 36072

Presentation of Case

A seventy-two-year-old woman entered the hospital complaining of itching of the skin and "indigestion."

Except for chronic visual difficulty she had been in good health until two weeks before admission, when she began to notice "gaseous indigestion" and itching of the skin. She had been subject to occasional episodes of indigestion for many years, but the attacks had been infrequent, not accompanied by pain and without relation to the intake of any particular food. This new discomfort, however, was much more severe, with epigastric burning and a feeling of pressure described as a "load on the stomach." This was accompanied by nausea and belching of foul-tasting gas, usually two or three hours after eating. About one week prior to entry she noticed that her urine was dark. She had always been somewhat constipated but noticed fewer bowel movements during this period; the stools seemed lighter in color and more bulky than usual. The epigastric distress grew worse during the week before admission, but the itching of the skin improved somewhat. There had been no anorexia, vomiting, chills, fever or pain other than that in the epigastrium. She did not drink alcoholic beverages, nor had she been exposed to any jaundiced person. She did not complain of jaundice on admission, but one examiner elicited the fact that about three weeks before admission she had

*Abbott, M. E. *Atlas of Congenital Cardiac Disease.* 62 pp. New York: American Heart Association, 1936. P. 52.

noticed jaundice but paid no particular attention to it.

The past history revealed several previous admissions to the hospital because of glaucoma and cataract, which had been treated with some improvement.

Physical examination on admission revealed an obese, moderately jaundiced woman in no discomfort. There were excoriations over the back and arms. No spider angiomas were found. The chest was clear. The heart was of normal size, with a Grade I systolic murmur at the base. The abdomen was large, fat and soft. The liver edge was barely palpable on deep inspiration and was questionably tender. The spleen was not palpable. There were no masses.

The temperature was 98.6°F., the pulse 72, and the respirations 20. The blood pressure was 200 systolic, 110 diastolic.

The urine had a specific gravity of 1.018 and gave a + test for albumin, a 0 test for sugar and a ++ test for bile. Urinary urobilinogen was present in a dilution of 1:64. The quantitative urobilinogen was 2.5 Ehrlich units per two hours. Examination of the blood showed a red-cell count of 5,000,000, with a hemoglobin of 13.5 gm., and a white-cell count of 6750, with 50 per cent neutrophils, 42 per cent lymphocytes and 8 per cent monocytes. Four stools were clay colored, and all were guaiac negative. The nonprotein nitrogen was 26 mg., and the total protein 6.71 gm. per 100 cc., with 4.36 gm. of albumin and 2.35 gm. of globulin, the cholesterol 223 mg., the cholesterol esters 80 mg., the phosphorus 4.3 mg. and the alkaline phosphatase 15.9 Bodansky units per 100 cc. A van den Bergh reaction was 9.6 mg. per 100 cc. direct, 14.0 mg. indirect. The prothrombin time was 16 seconds (normal, 17 seconds). A cephalin-flocculation test was + in twenty-four and ++ in forty-eight hours, the thymol turbidity 2.4 units, the thymol flocculation negative, the vitamin A 0.0 units, and the carotenoids 1.7 units per 100 cc.

X-ray films of the chest showed slightly prominent linear markings in both lungs and calcification within the proximal portion of the bronchial tree on both sides. There was mottled density in the left apical region. The heart was slightly enlarged, and the thoracic aorta widened, elongated and tortuous, with calcification. A plain film of the abdomen disclosed no definite abnormality. A gastrointestinal series showed a small hiatus hernia. There was a very small diverticulum extending from the second portion of the duodenum. A suggestion of slight extrinsic deformity of the second portion of the duodenum was noted, with displacement of that portion toward the midline and anteriorly. A definite mass, however, could not be made out in that area. The duodenal mucosa was normal.

On the ward the patient's condition remained essentially the same, with some increase in jaundice as evidenced by a further elevation in the van den Bergh reaction to 20.1 mg. per 100 cc. direct, 30.3 mg. indirect. Other blood chemical tests were essentially as before.

On the twenty-fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Walter Bauer*: We are concerned with a seventy-two-year-old woman, whose past medical history was negative except for the visual difficulties and infrequent attacks of "indigestion" described. The latter complaint had been present for years without associated symptoms and was not related to the ingestion of any particular food. Whether or not this "indigestion" of years' standing is just a red herring or whether it was related to the illness for which she came to the hospital is, of course, the question. On reading the history I found it difficult to decide whether this woman actually had pain. She described the epigastric burning as a "load on the stomach." The history as it stands is not very helpful. One wishes for an opportunity to ask the patient a few questions about the epigastric discomfort. Likewise, the physical examination is not helpful. In fact, the record as it stands contains only a minimum of information that aids one in making a diagnosis.

Only one thing is obvious: the patient was jaundiced. Therefore, I shall limit my discussion to the type of jaundice that she may have had. In doing so I am forced to rely more on laboratory data, particularly those pertaining to liver function, than is usually wise. I wondered, as did the person who took the history, whether this patient was suffering from the hepatogenous type of jaundice. As I review the various laboratory tests I find precious little in favor of such an interpretation. The total serum protein was normal, as was the albumin-globulin ratio. I also interpret the cephalin-flocculation, thymol-turbidity and thymol-flocculation tests

*Physician, Massachusetts General Hospital.

as being negative. I would expect one or more of these three tests to be positive with parenchymal liver disease, of the type produced by infectious hepatitis. It is of interest that the alkaline phosphatase was approximately 16 Bodansky units per 100 cc. — a slightly higher value than we usually see in hepatogenous jaundice. As a rule it does not exceed 10 units. This one bit of information leads me to argue in favor of an obstructive type of jaundice. Though the total serum cholesterol was normal, the cholesterol esters were definitely reduced — a metabolic abnormality that usually indicates the presence of hepatogenous jaundice. In fact, a lowering of the cholesterol esters may be the earliest indication of liver injury in certain intoxications. Though I may be in error, I shall consider the cholesterol data as representing a laboratory error. In any event I shall not interpret these values as indicating hepatogenous jaundice. The laboratory data pertaining to urobilinogen are also of interest. It was present in a dilution of 1:64 and was 2.5 Ehrlich units per two hours. These values are higher than normal and mean that bilirubin was getting into the gastrointestinal tract. Therefore I am forced to conclude that the patient did not have complete obstruction. Such values, however, are seen in patients with intermittent obstruction and hepatogenous jaundice. Though I am not too certain I shall assume on the basis of the laboratory data that I am dealing with the obstructive type of jaundice.

Which of the usual causes was responsible for the obstruction is, of course, the answer I seek. This case exemplifies the wisdom of an exploratory operation. In doing so we can assure ourselves that we were not overlooking a disease that can be cured. I personally am inclined to make a diagnosis of common-duct stone rather than carcinoma of the head of the pancreas, carcinoma of the biliary ducts, carcinoma of the gall bladder or an extrinsic tumor mass. I do not know that I can rule out carcinoma of the ampulla of Vater in the light of the urobilinogen finding. On occasion an intermittent type of obstruction will manifest itself if sufficient ulceration takes place. In this case four stools were examined, and none were guaiac positive. This is very much against carcinoma of the ampulla of Vater undergoing ulceration. I shall interpret the abnormal liver-function tests as favoring intermittent, extrahepatic, obstructive jaundice. The two exceptions are the normal total serum cholesterol and the low cholesterol esters. My final diagnosis is stone in the common duct.

I did not look at the x-ray films. I meant to, but I got going and forgot them. Is there anything in the chest films that might influence me?

Dr. Stanley M. Wyman: The heart shadow is enlarged, chiefly in the region of the left ventricle. The aorta is tortuous and calcified, consistent with some degree of hypertensive arteriosclerotic disease. Examination two months later shows a small amount of fluid in the left pleural cavity and probably fluid between the left lower and upper lobes. No other definite intrinsic disease is seen. The films of the abdomen are of poor quality and show no definite enlargement of any particular organ. I do not see any definite stones.

Dr. Bauer: How about the displacement?

Dr. Wyman: There is some displacement of the duodenum and an area of poor filling in the duodenum, but it probably represents poor filling rather than actual intrinsic disease. A small diverticulum is noted in the second portion of the duodenum.

Dr. Bauer: Is the displacement due to the diverticulum?

Dr. Wyman: No. I do not see any varices of the esophagus. There may be a small hiatus hernia.

Dr. Bauer: I shall stick to the diagnosis of stone in the common duct as being the most likely possibility.

Dr. Tracy B. Mallory: Are there any alternative diagnoses?

Dr. J. H. Means: I had the patient on the ward, and our line of reasoning was similar to Dr. Bauer's. I wrote, "While awaiting laboratory evidence to rule parenchymatous liver disease in or out, I am going to put extrahepatic obstructive jaundice, stone or pancreatic cancer as the first choice." Dr. Jones's group, particularly Dr. Volwiler, worked on this patient, and the question was whether or not all the laboratory data were significant. We held to the position that we badly needed a liver biopsy. Dr. Volwiler did not think there was enough space to make it safe. We tried to arrange a peritoneoscopy and get a biopsy in that fashion. A few days later I consulted Dr. Jones, believing that the obstruction was extrahepatic, and told him that I favored exploration, which had been deferred so that we might get a

liver biopsy. The peritoneoscopist was ill, and I asked Dr. Jones if we should wait until he recovered or go ahead with exploration without biopsy. Dr. Jones replied as follows:

> No conclusive diagnostic evidence is available in this case. The bulk of evidence is against any serious impairment of liver-cell function. I believe that another delay to get peritoneoscopic evidence is not justified. I advise exploration, preferably under spinal anesthesia, to avoid the effect of ether and any anoxia on a diseased liver. The anesthesia depends, of course, on the surgeon's decision. I think the chances are against an infectious hepatitis. It is important to find out now what the diagnosis is.

One of the clinical points that impressed us was that the patient never acted as if she were particularly sick, which I thought was against hepatitis, but we did not actually know what the diagnosis was until operation was performed.

Dr. Fiorindo A. Simeone: I was the person who guided the resident surgeon through the operation. Before operation we went through the same reasoning as Dr. Bauer. Dr. Bauer had one piece of information that we did not have preoperatively — namely, the low ratio of the cholesterol and cholesterol esters. However, subsequent determinations showed a ormal ratio, so I believe Dr. Bauer was correct in assuming that the first one was a laboratory error. My preoperative diagnosis was carcinoma of the extrahepatic biliary tract.

Clinical Diagnoses

Carcinoma of common duct.
Obstructive jaundice.

Dr. Bauer's Diagnoses

Cholelithiasis.
Common-duct stone.

Anatomical Diagnosis

Infectious hepatitis, epidemic type.

Pathological Discussion

Dr. Simeone: At operation the liver appeared normal grossly, but the common duct appeared larger than normal. Estimation varied between two and three times the normal diameter. No stones were felt within it. Since carcinoma of the head of the pancreas had not been ruled out we did not want to open the common duct at this stage of the operation and explored it transduodenally. No abnormalities were found in the duodenum or in the pancreas. The displacement of the duodenum was due to a benign cyst of the right kidney. We took a liver biopsy.

Dr. Mallory: This liver biopsy was a generous one, and we were quite sure of the findings. It showed a perfectly characteristic picture of severe infectious hepatitis.

Dr. Simeone: Postoperatively, the patient had some type of complication, but the jaundice steadily cleared despite the septic course.

Dr. Bauer: In the light of what was found at operation it is obvious that I attached too much significance to one test, the elevated alkaline phosphatase. I have never seen a value of 16 Bodansky units in a case of infectious hepatitis and therefore leaned heavily on it as indicating obstructive jaundice. In doing so I disregarded two important findings, — a normal serum total cholesterol and an increased urinary urobilinogen excretion, — which were in keeping with the correct diagnosis, infectious hepatitis. The low cholesterol esters would have been a third point favoring hepatitis, but in view of the inconsistent laboratory findings it is evident that we cannot rely upon them. I repeat that it is unwise and at times hazardous to depend solely on laboratory tests in making a diagnosis.

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MIDWINTER MEETING OF THE COUNCIL

The Council of the Massachusetts Medical Society held its regular midwinter meeting in the auditorium of the Boston Conservatory of Music on Wednesday, February 1, with 256 councilors present.

The Secretary announced the plan for collecting the recently assessed dues of $25 to the American Medical Association, stressing the point that members who were still in arrears at the end of January, 1951, would lose their membership in the American Medical Association but that their fellowship in the Massachusetts Medical Society would not thereby be jeopardized.

The Council was reminded that the law requires all physicians registered in the Commonwealth to register also with the clerk of the municipality or municipalities in which they intend to open offices. Failure to do so places them in the position of practicing medicine illegally.

Among the various reports of committees that were accepted, certain ones are of particular importance to the Society as a whole. The previous action of the Council in approving the establishment of a pilot multiphasic screening clinic was reaffirmed by the acceptance of the report of the Committee on Pilot Clinics. It is understood that this clinic actually represents a research problem.

The Committee on Hospitals and Professional Relations presented the Principles of Relationship Between Radiologists and Hospitals, which had been approved by the Board of Trustees of the American Hospital Association, the Radiological Inter-Society Committee, the Council on Medical Education and Hospitals of the American Medical Association, and the American College of Surgeons, and reaffirmed by the Massachusetts Hospital Association.

Since this action by the Massachusetts Hospital Association renders useless, for the present at least, further conferences with the Association, the committee recommended that further efforts to achieve the adoption of the recommendations of the Committee to Study Special Services be made at local levels.

The Council, on recommendation of the Committee on Council Rules and By-Laws, approved two changes in the by-laws. If accepted by the Society at the Annual Meeting, Chapter III, Section 5, will thus be changed to establish a minimum of six councilors from each district, and Chapter V, Section 2(b), to ease the requirements for membership of graduates of discontinued, foreign or unapproved schools from being licensed to practice medicine in "the United States or its territories for at least five years," to "the district from which he makes application for at least one year."

The recommendation of the Subcommittee of the Executive Committee on Blue Cross–Blue Shield Problems that the upper income limit for Blue Shield subscribers be raised to include the $3000 to $5000 income group provoked considerable discussion. It was adopted largely on the premise that such an adjustment, on the basis of the changed dollar value, simply brought the coverage back in line with the original concept of Blue Shield operations.

HOSPITALS, MEDICINES AND PREPAID MEDICAL CARE

THE popularity of such voluntary plans as Blue Cross and Blue Shield is evidence that a large number of people, especially those with moderate or low incomes, desire some form of prepayment plan to cover the major part of the cost of expensive illnesses. Furthermore, it also indicates a willingness, or at least acquiescence, on the part of participants in these or similar plans to support the private and business-like management of such organizations as long as they continue to provide in a satisfactory manner the services for which they have contracted. There can be little doubt that if such plans fail, the clamors for the Government to provide these functions will increase and become irrepressible.

It should be borne in mind that prepaid medical plans are essentially insurance plans. As in any insurance business, the value of all benefits plus administrative costs must, of necessity, be covered by the premiums paid in. If the total premiums paid are exceeded by any increase in the amount of the benefits paid out, this must be compensated for either by a reduction in the benefits or by an increase in the premiums.

The steady rise in the cost of hospitalization has placed a great burden on the prepayment plans, and only part of this increase could be met by any relatively small or acceptable increase in the premiums. This has necessitated additional payments by the participants for part of their hospitalization costs.

The cost of many kinds of medications has now also increased markedly, and payments for such medications are generally included among the benefits of prepayment medical programs. This is true, however, only when they are administered during the period of hospitalization. This provision has become a source of abuse by many physicians and is potentially a very serious one. Patients who could readily be treated at home and many who could equally well be managed on an ambulatory basis or are actually being treated by the physician in his office are sent into hospitals to occupy beds and to make use of hospital services that they do not need, simply to obtain the benefits of some expensive medication. The abuse is further compounded by the prescription of several expensive agents simultaneously or in sequence. The fault, of course, is not entirely with the physician, who may rightly regard this as the only way by which his patient can derive the benefit from a therapy that is more expensive than he can afford. Most of these contracts, like those of the Blue Cross and Blue Shield, do not cover treatment outside hospitals. The inclusion of such benefits to office patients or to those treated at home would undoubtedly be subject to even greater abuses and would tremendously increase the cost of medical prepayment plans, possibly beyond the reach of a large proportion of those now participating.

Just how widespread the abuse of the hospitalization provisions merely for the purpose of obtaining expensive medicaments has become is difficult to judge. It is not difficult to anticipate, however, that the release of important drugs such as Cortisone and ACTH for general distribution at necessarily high cost could within a very brief period completely exhaust the resources of any prepayment medical organization. Recent experiences with new antibiotics are offering a good preview of what is in the offing. It would be well for hospitals, physicians and directors of medical-care organizations to give this matter serious consideration and to make some provisions for curtailing these abuses before they kill the goose that laid the golden egg. Politicians interested in solving all medical problems of finances in one fell swoop are waiting eagerly for just such developments. The medical profession, if it is to maintain any independence from political control, must help to avoid the abuses by solving these problems in time to avoid disaster.

BLEEDING CENTER OPENS

ON JANUARY 11 the Regional Bleeding Center of the Massachusetts Red Cross blood program was officially opened by General Marshall, head of the Red Cross, and other dignitaries. This opening is of fundamental importance to the medical profession in Massachusetts.

In this center blood will be collected from donors in the Boston area. To it will come blood collected

by the three mobile units now conducting regular service throughout the Commonwealth. Here it will be processed by a staff of technicians and then redistributed on a basis of need throughout the State. Since the inauguration of the blood program, the aim of the Red Cross and of the Advisory Committee for the Red Cross Blood Program of the Massachusetts Medical Society has been to send the major portion of the blood collected to the hospitals where it is impractical to maintain blood banks and yet where blood is badly needed. With the opening of the new center this policy will be continued, but will be amplified as the blood on hand increases.

In 1949 the Red Cross produced approximately 50,000 pints of blood in a state in which the present demand is 200,000 pints a year. The rest was collected in private banks. The present problem of the Red Cross is to produce blood in sufficient quantity to fill the demands made upon it by local chapters when the relatives of patients needing blood appeal to those chapters for aid. Another has been to keep an adequate supply in the local depots and hospitals to cover their needs.

With the addition of the third mobile unit and the opening of this center, the supply of blood will increase and the service to doctors and patients will improve if the medical profession in Massachusetts recognizes the part it has to play in making the Red Cross program work. This program is not designed to replace existing blood banks, but to supplement their supply. It is being carefully supervised by the Massachusetts Medical Society and has been approved by the Society. There are several things that physicians should do to ensure an adequate supply of blood. The first is to work with the Red Cross chapters locally, helping them with their publicity and their technical problems, and helping to co-ordinate their efforts with those of the local hospitals so that the system will work smoothly. The second is to see to it that every patient receiving Red Cross blood knows about it, and his family recognizes its moral obligation to replace the blood, whether by making an appointment with the mobile unit or by going to the Boston center, which is open six days a week. Through these efforts patients will be relieved of a great expense and a great worry. The availability of blood will offer a significant improvement in medical care. This is an opportunity for all physicians to show what voluntary medicine can do and is doing for the public.

THE COMMONWEALTH FUND IN 1949

THE thirty-first annual report of the Commonwealth Fund makes profitable reading for all who are interested in the advance of medicine as a science and an art. This publication of the various grants and fellowships awarded in 1949 emphasizes the debt owed by the medical profession and the public it serves to the founder of the Fund, whose goal—"to do something for the welfare of mankind"—appears, as always, to have been realized in achievements of lasting value.

With commendable frankness the report puts its finger on some of the inadequacies of medical care as it now prevails, but, unlike the planners in Washington, it expresses the ideals of medical practice in terms with which no conscientious physician can differ. "Specifically, without leaving out anything that is now essential to good medicine, they add new dimensions to it: breadth, to include more attention to the patient's environment; depth, to include some comprehension of his inner motivations; and duration, to relate the patient's present condition to his past and future."

As an initial step to the attainment of these purposes, attention is first of all concentrated on medical education, with particular emphasis on the relation between psychiatry and such clinical fields as general medicine and pediatrics; this concept of medical-psychiatric teaching has been applied in Boston to a joint program at Harvard Medical School and the Peter Bent Brigham Hospital, with support from the Commonwealth Fund in the amount of $31,656, and at University of Cincinnati College of Medicine with an award totaling $46,600. The grants for these projects and for others throughout the country add up to the impressive figure of $246,256 disbursed to aid medical education.

Logically, the program next focuses on experimental health services and public-health and hospital activities. Grants of more than $420,000 in

these fields included $35,000 for extension of a home-care plan at the Montefiore Hospital in New York City and $59,760 for medical care of indigents by the Department of Public Health in Richmond, Virginia.

To train candidates in the fields in which it is particularly interested, the Fund has awarded fellowships amounting to $131,800, whose purposes are as follows: to prepare young men for new patterns of work, exemplified in the early child-guidance clinics; to increase professional competence in fields in which standards are being raised, as in public-health and hospital service; and to expand professional groups, such as the psychiatrists, now subjected to growing demands. In this country an interesting aspect of these fellowships in medicine and allied fields is the grant of $10,000 a year for three years awarded for the education of Negro physicians. Abroad, fellowships in psychiatric social work were given to students from China, India, South Africa and Norway.

Support for medical research consisted of generous allotments, totaling nearly $500,000, to twenty-three medical schools and hospitals throughout the United States. Typical projects included neurophysiologic research, investigation of basic biologic phenomena and a study concerning a baffling problem of surgical technic.

In addition to the activities enumerated above, the Commonwealth Fund fellowships for candidates from the British dominions and colonies were continued and expanded, and publication of books and pamphlets was sponsored, six titles being added to the already impressive list of works published by the Fund. For work in the field of mental health, Mildred C. Scoville received the Lasker Award for 1949.

The obligation of physicians to the Commonwealth Fund is all the more gratefully acknowledged by those who are loath to exchange this kind of support for the kind that presupposes submission to governmental dictation. The value of the grants continuously awarded by the Fund, as well as those of similar organizations, is amply demonstrated by the record of the progress achieved under their sponsorship; perhaps their importance is emphasized by the curious lack of reference, in all the arguments of the necessity for compulsory health insurance, to the vital part of private philanthropy in the advance of the medical sciences.

Dr. A. B. Chapman, of Galesburg, Illinois, proposes to publish, by subscription, "The principles and practice of surgery — developing the principles of the reformed practice, and conforming strictly to the treatment recommended" — that is, according to the steam, pepper and lobelia system!

Boston M. & S. J., *February 13, 1850*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

All members should be reminded that the proportion of the refund returned to each district society is based on the number of dues paid by March 1 in that district, and also that the names of members who have not paid their dues by March 1 are automatically removed from the mailing list of the *Journal* until such dues are paid.

ELIOT HUBBARD, JR., *Treasurer*

DEATH

HEWITT — Wright P. Hewitt, M.D., of Cambridge, died on February 2. He was in his forty-fourth year.

Dr. Hewitt received his degree from Harvard Medical School in 1932. He was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

His widow survives.

MISCELLANY

BRIGGS CLINIC AT BOSTON STATE HOSPITAL

A new psychiatric outpatient department affiliated with the Boston State Hospital, the Briggs Clinic, for the diagnosis and treatment of emotional problems in adults, was opened on February 15, in temporary quarters located in the East Office Building at the Paxton Street Gate of the Hospital. The clinic, sponsored by Dr. Walter E. Barton, superintendent of the Hospital, will operate on a full-time basis under the direction of Dr. James Mann, senior psychiatrist of the Hospital, with a staff of two social workers, a psychologist and two clerks.

The clinic honors the name of the late Dr. L. Vernon Briggs, a pioneer in fostering the creation of clinic facilities for psychiatric patients.

The aim of the clinic is to apply principles of preventive mental hygiene to the treatment of emotional problems before they become so disabling as to require hospitalization. Policies have been formed in such a manner as to provide maximal assistance to the individual patient. Copies of these aims and policies may be obtained on request from the Boston State Hospital or from the Briggs Clinic.

Appointments may be obtained by telephone (GEneva 6-6000).

CORRESPONDENCE

QUININE AS AN ALLERGEN

To the Editor: The article "Quinidine as a Cause of Thrombocytopenic Purpura," by Dr. Norcross, which appeared in the January 12 issue of the *Journal*, offers a timely opportunity to remind our confreres that the quinine group is potently allergenic. I have seen diffuse purpura, involving skin and mucous membranes, follow a single dose of quinine sulfate in a hypersensitive person.

S. P. Lucia, M.D.
Professor of Medicine
University of California

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Industrial Toxicology. By Lawrence T. Fairhall, scientist director, Public Health Service, Federal Security Agency, and chief, Industrial Hygiene Laboratory, Industrial Hygiene Division. 8°, cloth, 483 pp. Baltimore: Williams and Wilkins Company, 1949. $6.00.

This book constitutes a reference manual on the toxicity of substances used in industry. The text is divided into two parts: inorganic substances and carbon compounds. The new substances used in industry, some of which are not toxic, have been included under the proper classification. Under each heading the characteristics, analysis, uses and toxicity, are briefly discussed, and the available literature is surveyed, summarized and evaluated. Lists of pertinent references are appended to the various topics. The material is arranged alphabetically in each part, and there is a good index. The book is well published and is recommended as a reference source for all medical libraries.

Group Medicine & Health Insurance in Action. By Robert E. Rothenberg, M.D., chairman, Medical Group Council, The Health Insurance Plan of Greater New York, and chairman, Central Medical Group of Brooklyn; and Karl Pickard, M.D., member, Medical Control Board, Health Insurance Plan of Greater New York, and secretary, Central Medical Group of Brooklyn. Assisted by Joel E. Rothenberg, J.D., member, New York Bar, attorney, Medical Group Council, Health Insurance Plan of Greater New York, and administrative counsel, Central Medical Group of Brooklyn. With an introduction by George Baehr, M.D. 8°, cloth, 278 pp. New York: Crown Publishers, 1949. $5.00.

This book describes in detail all aspects of the Central Medical Group of Brooklyn, organized by a group of physicians, who have served more than fourteen thousand persons under a comprehensive health plan during the past two years. The authors acknowledge the assistance as contributors of twenty-six physicians of the Brooklyn group. The book is well published, except that it lacks an index, which is compensated for, to a certain extent, by a detailed table of contents. The book should be in all collections on the subject. It relates the experience of a going prepaid medical practice group.

Bridges' Dietetics for the Clinician. By Harry J. Johnson, M.D. Fifth edition. 8°, cloth, 898 pp., with 84 tables. Philadelphia: Lea and Febiger, 1949. $12.00.

This new edition of a well known book has been revised and brought up to date, only the practical advances in the field of nutrition being included. The text is the joint work of twenty-seven contributors. The material is divided into two parts: general considerations and the dietetic management of diseases of adults. There is a long appendix, presenting various tables on weight, foods and vitamins. The first part considers digestion, vitamin factors in diet, acid-base factors in nutrition, the classification, structure and practical evaluation of foods, tabulation of food factors, food adjuncts and supplementary methods of feeding. The book is well published and should be in all medical libraries and available to all physicians and dietitians.

A Companion in Surgical Studies. By Ian Aird, Ch.M., F.R.C.S., professor of surgery in the University of London, and director of the surgical unit, Postgraduate Medical School of London. 8°, cloth, 1060 pp. Baltimore: Williams and Wilkins Company, 1949. $15.00.

This book is intended for the postgraduate student of surgery. It is based on the lecture notes of the author, supplemented by the pertinent literature on the subject. The material is arranged by regions and organs of the body and is documented throughout with selected references. The text is concluded with a comprehensive index. The publishing is well done. The book was printed in Great Britain.

Outlines of Internal Medicine. Edited by C. J. Watson, M.D., head, Department of Medicine, University of Minnesota Medical School. Sixth edition. 4°, cloth, 434 pp. Dubuque, Iowa: Wm. C. Brown Company, 1949. $12.00.

This popular, useful book has now gone through six editions since it was first published in 1946. The material is arranged in outline form and presents as concisely as possible the most significant information available on the pathological physiology, diagnosis and treatment of disease. The *Outlines* are designed primarily as a systematic course of reading, to be correlated with biweekly class clinics given during the junior year in medicine.

NOTICES

ANNOUNCEMENTS

Dr. Albert Cohen announces the opening of an office at 1093 Beacon Street, Brookline, for the practice of pediatrics and pediatric cardiology.

Dr. Eugene Guralnick announces a change of address from 87 Maple Street, Roxbury, to 18A Forest Street, Cambridge.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the Boston City Hospital House Officers Association will be held in the Dowling Amphitheater of the Boston City Hospital on Tuesday, February 21, at 7 p.m. Dr. Edwin B. Astwood will speak on the subject "Diseases of the Thyroid Gland."

All interested persons are invited to attend.

94TH INFANTRY DIVISION LECTURE

The eleventh lecture in the series sponsored by the 94th (Bay State) Division will be held in the amphitheater of the Evans Memorial, Massachusetts Memorial Hospitals, 750 Harrison Avenue, Boston, on Thursday, February 23, at 8 p.m.

Dr. Francis B. Carroll, deputy chief medical director of the Veterans Administration, New England and New York areas, will speak on the subject "Studies in Reference to Meningococcal Meningitis."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will be shown during this period.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held in Boston on Wednesday, March 8.

PROGRAM

2:30–5:00 p.m. Amphitheater B, Harvard Medical School. Presentations by the Staff of The Children's Medical Center.

7:30 p.m. Longwood Towers, Various Aspects of Adolescence.

PHI LAMBDA KAPPA LECTURE

The annual lecture of the Beta Chapter of Phi Lambda Kappa Fraternity will be presented in McClellan Hall, Jefferson Medical College, 1025 Walnut Street, Philadelphia, on Wednesday, March 8, at 8 p.m. Dr. Joe Vincent Meigs, clinical professor of gynecology, Harvard Medical School, and chief of the Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital, Boston, will speak on the subject "Carcinoma of the Cervix."

BETH ISRAEL HOSPITAL LECTURES

The following lectures will be delivered at 7:30 p.m. on the dates indicated at the Beth Israel Hospital in Boston:

March 1. Chemotherapeutic Agents in Leukemia and Lymphoma. Dr. Sidney Farber.
March 8. Pulmonary Circulation in Health and Disease. Dr. Lewis Dexter.
March 15. Mechanism of Renal Water and Electrolytes. Dr. Charles H. Burnett.
March 22. Electrolyte Imbalance of Diabetic Ketosis. Dr. Allan M. Butler.
March 29. Modern Management of Syphilis. Dr. G. Marshall Crawford.

PUBLIC SEMINARS IN CHEMOTHERAPY

Public seminars in chemotherapy, sponsored by the Division of Laboratories and Research, The Children's Hospital, and the Children's Cancer Research Foundation, will be given, at 4 p.m. on the dates indicated below, by Dr. Harry Eagle, of the Division of Experimental Therapeutics, Microbiological Institute, National Institutes of Health, Bethesda, Maryland. The subjects of the seminars are as follows:

March 10. Bacterial Resistance and Drug Synergism.
March 24. Participation of the Host in the Therapeutic Activity of Antibiotics.
April 7. The Problem of Treatment Failure with the Antibiotics.

Those who would like to attend the seminars should write to Mrs. Christine McGachie, Secretary, 300 Longwood Avenue, Boston, or telephone BEacon 2-7800, so that suitable arrangements may be made.

AMERICAN COLLEGE OF CHEST PHYSICIANS PRIZE-ESSAY AWARD

The American College of Chest Physicians offers an annual cash prize award of $250 for the best original contribution, preferably by a young investigator, on any phase of chest disease. The prize is open to contestants of foreign countries as well as those residing in the United States. The winning contribution will be selected by a board of impartial judges, and the first award will be made at the forthcoming annual meeting of the College to be held in San Francisco, June 22-25.

The College reserves the right to invite the winner to present his contribution at the annual meeting, and to publish the essay in its official publication, *Diseases of the Chest*. Contestants are advised to study the format of *Diseases of the Chest* for length, form and arrangement of illustrations to guide them in the preparation of the manuscript.

The following conditions must be observed: five copies of the manuscript, typewritten in English, should be submitted to the office of the American College of Chest Physicians not later than May 1, 1950; the only means of identification of the author or authors shall be a motto or other device on the title page and a sealed envelope, bearing the same motto on the outside, enclosing the name of the author or authors.

Additional information may be obtained from the Executive Secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

NATIONAL FOUNDATION FOR INFANTILE PARALYSIS FELLOWSHIPS

The National Foundation for Infantile Paralysis is offering fellowships to physicians for one academic year of study leading to a degree of master of public health at a school of public health approved by the American Public Health Association and clinical fellowships in physical medicine, for one to three years, to physicians who wish to prepare for certification by the American Board of Physical Medicine.

Eligibility requirements include United States citizenship, graduation from a Class A medical school, completion of an internship of not less than one year, license to practice medicine in one or more states and sound health. In addition, candidates for clinical fellowships in physical medicine must be forty years of age or younger.

Financial benefits are flexible and will be arranged according to individual needs. Candidates for the two classes of fellowships will be selected competitively by the Committee on Fellowships in Public Health and the Committee on Fellowships in Physical Medicine composed of physicians certified by the American Board of Physical Medicine.

In accepting a public-health fellowship each recipient must agree to work as a public-health officer in a state or local health department in the United States or its territories for at least two years. Those accepting the fellowships in clinical medicine must agree to practice as specialists in physical medicine in the United States or its territories for a minimum of two years and must have completed three years of clinical study, both requirements being necessary for qualification for certification by the American Board of Physical Medicine.

Additional information and applications may be obtained from the Professional Education Division, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.
JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.
FEBRUARY 18. Springfield Hospital. Page 196, issue of February 2.
FEBRUARY 20. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.
FEBRUARY 20. Hartford Medical Society. Page 160, issue of January 26.
FEBRUARY 20–23. American Academy of General Practice. Page 252, issue of August 11.
FEBRUARY 21. South End Medical Club. Page 233, issue of February 9.
FEBRUARY 21. Springfield Hospital. Page 196, issue of February 2.
FEBRUARY 21. Boston City Hospital House Officers' Association. Page 269.
FEBRUARY 23. Massachusetts Trudeau Society. Page 233, issue of February 9.
FEBRUARY 23. 94th Infantry Division Lecture. Page 269.
FEBRUARY 27. Boston Chapter of the American Federation for Clinical Research.
MARCH 1. Beth Israel Hospital Lecture. Notice above.
MARCH 6. New England Cardiovascular Society. Page 724, issue of November 3.
MARCH 8. New England Pediatric Society. Page 269.
MARCH 8. Phi Lambda Kappa Lecture. Notice above.
MARCH 8. Beth Israel Hospital Lecture. Notice above.
MARCH 9. Neck Tumors — Problems of Diagnosis and Management. Dr. Joseph Tartakoff. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
MARCH 9–11. American Goiter Association. Page 234, issue of February 9.
MARCH 10. Public Seminar in Chemotherapy. Notice above.
MARCH 14. New England Society of Anesthesiologists. Page 234, issue of February 9.
MARCH 15. Beth Israel Hospital Lecture. Notice above.
MARCH 22. Beth Israel Hospital Lecture. Notice above.
MARCH 23. Cornell Alumni Day. Page 234, issue of February 9.
MARCH 24. Public Seminar in Chemotherapy. Notice above.
MARCH 29. Beth Israel Hospital Lecture. Notice above.
APRIL 7. Public Seminar in Chemotherapy. Notice above.
APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.
APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.
APRIL 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.
MAY 3. Norfolk District Medical Society Anniversary Dinner.
MAY 4. Suffolk District Censors' Meeting. Page 234, issue of February 9.
MAY 14–19. International and Fourth American Congress of Obstetrics and Gynecology. Page 160, issue of January 26.
MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
MAY 24–26. American Association of Genito-Urinary Surgeons. Page 234, issue of February 9.
JUNE 22–25. American College of Chest Physicians. Notice above.
JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.
JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.
AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.
SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.
SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.
NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

(*Notices concluded on page xi*)

NOTICES (*Concluded from page 270*)

District Medical Societies

NORFOLK

February 28.
March 28.
May 3. Anniversary Dinner.

SUFFOLK

May 4. Censors' Meeting.

Calendar of Boston District for the Week Beginning Thursday, February 23

Thursday, February 23
*9:00-10:00 a.m. Grand Rounds. House of the Good Samaritan.
*8:00 p.m. 94th Infantry Division Lecture. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals.

Friday, February 24
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

Monday, February 27
*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*8:00 p.m. Boston Chapter of the American Federation for Clinical Research, White Building, Amphitheater 3A, Massachusetts General Hospital.

Tuesday, February 28
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, March 1
*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.
*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.
*7:30 p.m. Chemotherapeutic Agents in Leukemia and Lymphoma. Dr. Sidney Farber. Beth Israel Hospital.

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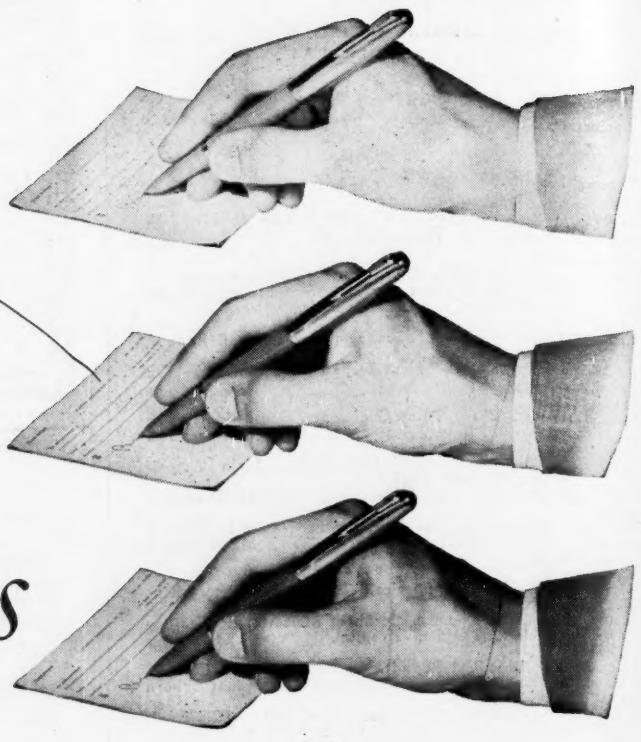

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